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Targeting the orexin/hypocretin system for the treatment of neuropsychiatric and neurodegenerative diseases: From animal to clinical studies

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ABSTRACT

Orexins (also known as hypocretins) are neuropeptides located exclusively in hypothalamic neurons that have extensive projections throughout the central nervous system and bind two different G protein-coupled receptors (OX1R and OX2R). Since its discovery in 1998, the orexin system has gained the interest of the scientific community as a potential therapeutic target for the treatment of different pathological conditions. Considering previous basic science research, a dual orexin receptor antagonist, suvorexant, was the first orexin agent to be approved by the US Food and Drug Administration to treat insomnia. In this review, we discuss and update the main preclinical and human studies involving the orexin system with several psychiatric and neurodegenerative diseases. This system constitutes a nice example of how basic scientific research driven by curiosity can be the best route to the generation of new and powerful pharmacological treatments.

1. Introduction

The orexin system, also known as hypocretin system, was concurrently discovered in 1998 by two different research groups. Takeshi Sakurai and colleagues discovered two peptides that stimulated food intake in rats. These peptides and correspondent receptors were termed "orexins" (orexin-A and orexin-B; orexin receptor-1 and orexin receptor-2) (Sakurai et al., 1998). At the same time, Luis de Lecea and co-workers described a hypothalamus-specific mRNA which encoded the precursor of two similar peptides. They named these peptides "hypocretins" (hypocretin-1 and hypocretin-2; hypocretin receptor-1 and hypocretin receptor-2) (de Lecea et al., 1998). A few months later, it became clear that the orexin and the hypocretin systems were different terms for the same neurotransmission system (Nisoli et al., 1998). Altogether, the names "orexin" and "hypocretin" are currently used as synonyms in the scientific literature. To avoid potential confusion, the term "orexin" will be used throughout this review.

Orexins were originally known for their role in the central regulation of feeding (Sakurai et al., 1998) and the stimulation of arousal (Hagan et al., 1999). However, cumulative research has provided new evidence about the relevance of the orexin system in many physiological and pathological conditions (Jacobson et al., 2022). Along the present review we will summarize and discuss several genetic animal models and behavioral endophenotypes of the different psychiatric disorders in which orexins have been reported to be involved, as well as related clinical findings.

2. The orexin system

2.1. Orexins and receptors

Orexin-A (OXA) and orexin-B (OXB) are neuropeptides synthesized by neuronal cells primarily found in the lateral hypothalamic area (LHA), which includes the perifornical, lateral, posterior and

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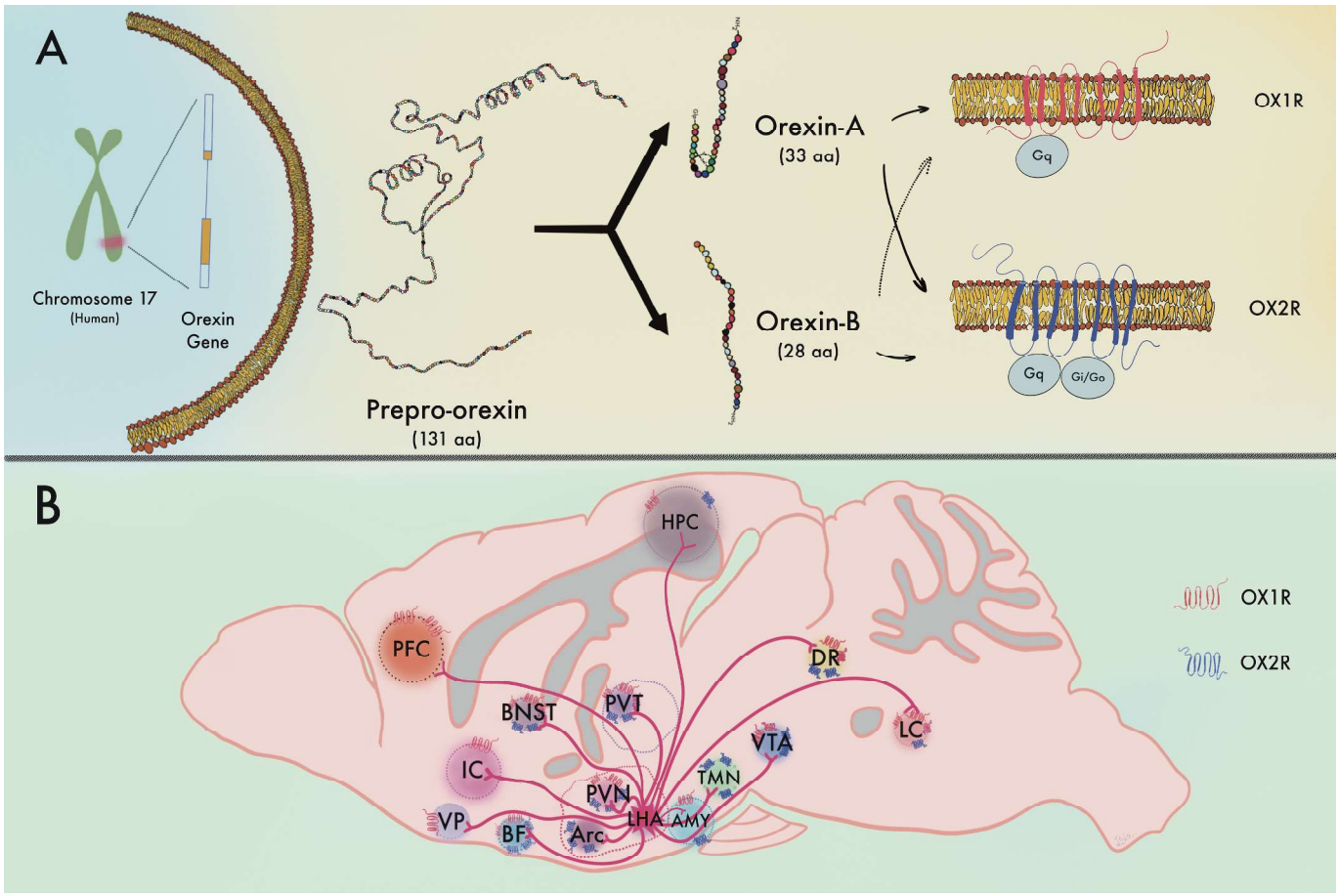

Fig. 1. Schematic representation of the orexin peptides biosynthesis and the neurobiological distribution of the orexin system in the brain. (A) Orexins are two neuropeptides derived from the same precursor, that interact with OX1R and OX2R. Orexin-A presents equal, high affinity for OX1R and OX2R, whereas Orexin-B interacts with a similar, high affinity for OX2R but lower (~ 10-fold) for OX1R. (B) Orexin neurons from the LHA project to several brain areas which present different density of OX1R (pink) and OX2R (blue). AMY, amygdala; Arc, arcuate nucleus; BF, basal forebrain; BNST, bed nucleus of the stria terminalis; DR, dorsal raphe; HPC, hippocampus; IC, insular cortex; LHA, lateral hypothalamic area; LC, locus coeruleus; PFC, prefrontal cortex; PVN, paraventricular nucleus in the hypothalamus; PVT, paraventricular thalamus; TMN, tuberomammillary nucleus; VP, ventral pallidum; VTA, ventral tegmental area.

dorsomedial nuclei of the hypothalamus (Sakurai et al., 1998; de Lecea et al., 1998). These cells express a single-gene localized on the human chromosome 17q21, that encodes the prepro-orexin, a 131-residue polypeptide (Sakurai et al., 1999). By enzymatic cleavage of this common precursor, both orexins are synthesized. OXA is a 33-amino acid peptide with two intramolecular disulphide bridges within the N-terminal, whereas OXB is a linear 28-amino acid peptide (Fig. 1). These neuropeptides share 46% homology (Sakurai et al., 1998). Orexin receptor-1 (OX1R; 425 amino acids) and orexin receptor-2 (OX2R; 444 amino acids) are widespread distributed across the brain and, to a lesser extent, in peripheral tissues (Peyron et al., 1998). Both receptors belong to the G protein-coupled receptor (GPCR) superfamily with seven transmembrane domains. In humans, OX1R and OX2R are located at chromosomes 1 and 6, respectively, and have 64% amino acid identity with each other (Kukkonen et al., 2002). OXA shows similar binding affinity for both receptor subtypes, whereas OXB is ~ 10-fold selective for the OX2R versus the OX1R (Sakurai et al., 1998). Moreover, the genetic and molecular organization of both peptides and receptors amongst vertebrates are highly similar, thus highlighting the strong evolutionary pressure exerted to preserve structural integrity and functions of the orexin system (Wong et al., 2011).

Orexin signaling is complex and can change depending on the cell type and environment (Kukkonen and Turunen, 2021). As explained before, OX1R and OX2R display the typical intracellular signaling through G-proteins, although only a few studies have focused on this coupling due to technical difficulties (Kukkonen and Leonard, 2014). Growing evidence support that the major primary signaling transducer for orexin receptors is associated with Gq proteins. This statement is inferred by a strong coupling to the Gq-mediated responses, consisting of a Ca^{2+} elevation and a phospholipase C activation (Johansson et al., 2007; Putula et al., 2014). The G-protein families Gi/o and Gs have also been implicated in the orexin signaling (Karteris et al., 2001), as well as the possibility of making heteromeric complexes with other GPCRs, at least in recombinant systems (Wang et al., 2019a; Raïch et al., 2022). Downstream signal pathways mainly induce neuroexcitatory activity as a consequence of Ca^{2+} increase. This ion elevation is caused by extracellular Ca^{2+} entrance through the modulation of membrane ion channels, as well as Ca^{2+} release from intracellular vesicles (van den Pol et al., 1998). Also, gene expression is modified through the activation or inhibition of protein kinases, mainly including mitogen-activated protein kinases and protein kinase A (Selbach et al., 2010; Guo and Feng, 2012). Arachidonic acid and phosphatidic acid are also synthesized via phospholipase A2 and D, respectively, downstream the orexin receptor activation (Turunen et al., 2010; Jäntti et al., 2012). These metabolites have a key role in the activation of different cation channels and protein kinases (Jang et al., 2012). The endocannabinoid 2-arachidonoylglycerol (2-AG) is also synthesized by diacylglycerol hydrolysis following orexin receptor activation. 2-AG is known to be a key regulator of neurotransmitters release (Haj-Dahmane and Shen, 2005), and mediates several physiological effects of orexins (Berrendero et al., 2018).

2.2. Neurobiological distribution

Orexin neurons are localized restrictively in the LHA, as described before. Deciphering the projections to other brain areas (i.e. outputs) is essential to elucidate the specific role of orexins in neuronal and behavioral regulation. However, it is also relevant to identify afferent neurons that modulate the activity of the orexin system (i.e. inputs) by releasing either excitatory or inhibitory neurotransmitters (Li and de Lecea, 2020).

In this sense, a key study developed by Sakurai and colleagues identified the amygdala, basal forebrain, preoptic area, raphe nuclei, ventromedial, dorsomedial and paraventricular nucleus in the hypothalamus (PVN), septum, infralimbic and prelimbic cortex, nucleus accumbens (NAc) shell and bed nucleus of the stria terminalis (BNST), as the main brain regions that modulate the activity of orexin neurons (Sakurai et al., 2005). Moreover, orexin neurons can be anatomically subdivided into at least two separate subpopulations, which correlate with the different brain projections and the corresponding physiological functions (Harris and Aston-Jones, 2006; Sagi et al., 2021). One subpopulation is localized in the lateral hypothalamus and sends projections to the ventral tegmental area (VTA) and NAc, thus regulating motivation and reward (Harris et al., 2005; Richardson and Aston-Jones, 2012). Conversely, orexin neurons residing in the perifornical and dorsomedial hypothalamus modulate arousal and response to stress, since projections reach related areas, such as the locus coeruleus (LC) and the tuberomammillary nucleus (Estabrooke et al., 2001; Nollet et al., 2011). Nevertheless, these orexinergic subpopulations are not completely separated since they remain intermingled (Iyer et al., 2018).

Peyron and colleagues illustrated the distribution and relative density of orexin fibers in the rat brain (Peyron et al., 1998) (Fig. 1). These results were confirmed by latter efforts (Nambu et al., 1999; Marcus et al., 2001), which highlighted a broad distribution of the orexin system throughout the whole brain. Additionally, orexin projections to peripheral tissues, such as the adrenal glands, kidneys, lungs, testis, ovaries, pituitary, jejunum, and thyroid, were also reported (Jöhren et al., 2001; Tsunematsu and Yamanaka, 2012). Given the controversial quality and selectivity of OX1R and OX2R antibodies, these key studies deciphering the orexin system distribution have directly measured orexin peptides immunoreactivity and the pattern of expression of mRNA for both orexin receptors. The different brain areas receiving orexin projections have been classified according to the most relevant function in which they have been involved:

Sleep-wake cycle homeostasis: the transition and maintenance of the sleep-wake cycle involve several neurotransmission systems and brain structures. Noradrenergic neurons of the LC receive the densest extrahypothalamic projections from orexin neurons (Peyron et al., 1998). OX1R is abundantly expressed in the LC, while OX2R expression is lower (Marcus et al., 2001). For that reason, OXA is much more efficient than OXB in depolarizing noradrenergic neurons from newly born mice (van den Pol et al., 2002). Orexin projections also achieve serotonergic neurons of the raphe nuclei (Peyron et al., 1998), specifically those neurons localized in the dorsal raphe portion (Lee et al., 2005). Both orexin receptors are present in this region (Marcus et al., 2001), although OX2R has a more pronounced effect in depolarizing serotonergic neurons (Soffin et al., 2004). Tuberomammillary nucleus neuronal cells synthesize histamine, a monoaminergic neurotransmitter classically related to sleep-wake cycle regulation in the central nervous system (CNS) (Ramesh et al., 2004). Orexin neurons from the LHA send abundant projections to this region (Peyron et al., 1998). OXR2 is much more expressed than OX1R, thus indicating a similar effect of OXA and OXB in depolarizing histaminergic neurons (Marcus et al., 2001; Eriksson et al., 2001). Acetylcholine (ACh) is another key modulator of the sleep-wake cycle. The largest collection of ACh neurons is localized in basal forebrain (Woolf, 1991), which includes several nuclei receiving abundant projections from the LHA (Peyron et al., 1998). Although OX1R and OX2R are equivalently expressed (Marcus et al., 2001), cholinergic neurons in the basal forebrain are activated mainly via OX2R in brain preparations (Eggermann et al., 2001). In addition, orexin inputs to brainstem cholinergic neurons also have an important role in the regulation of sleep-wake states (Kim et al., 2009). Specifically, cholinergic neurons of the pedunculopontine tegmentum are a key element of ascending arousal systems, presenting both orexin receptors although OX1R is more prominent in such region (Marcus et al., 2001). The paraventricular thalamus (PVT), which is also involved in the regulation of the sleep-wake cycle, expresses both orexin receptors (Marcus et al., 2001), although OXA and OXB excite postsynaptic neurons in this area likely through the activation of OX2R (Ishibashi et al., 2005).

Reward and motivation: reward-related disorders such as addictions, involve diverse brain structures which receive orexin projections from the LHA including the VTA (Peyron et al., 1998). In this region, OX1R and OX2R have been similarly identified (Marcus et al., 2001) and both orexin peptides potentiate excitatory synapses in the VTA neurons (Korotkova et al., 2003). Moreover, intracerebroventricular (icv) administration of OXA selectively activates dopaminergic neurons of the caudomedial VTA that project to the medial prefrontal cortex (mPFC) and the NAc shell (Vittoz et al., 2008). The NAc solely expresses the OX2R (Marcus et al., 2001). Another reward-related structure is the ventral pallidum. This area receives dense projections from orexin neurons with the particularity that only OX1R is expressed in this structure (Peyron et al., 1998; Marcus et al., 2001). The insular cortex, a less understood region in brain functional knowledge, has been related to rewarding properties of drugs of abuse (Hollander et al., 2008) and mainly presents OX1R (Marcus et al., 2001).

Stress resilience: the amygdala and the PVN are among the main regions that regulate stress. The amygdala involves diverse nuclei that mainly express OX1R, except for the lateral amygdala in which OX2R is much more abundant than OX1R (Marcus et al., 2001). Importantly, the amygdala also receives indirect inputs from the orexin system through noradrenergic neurons from the LC (Sears et al., 2013) and serotonergic neurons from the dorsal raphe (Hasegawa et al., 2017). The PVN shows an abundant expression of both orexin receptors, although OX2R has a prominent role in this nucleus (Marcus et al., 2001).

Feeding behavior and metabolism: the main brain structure receiving orexin projections involved in feeding and body weight regulation is the arcuate nucleus. Neurons in this area mainly express OX2R (Marcus et al., 2001). Also, the BNST receives dense projections from the LHA (Peyron et al., 1998) and regulates feeding behavior, among many other functions such as reward and arousal. Both orexin receptors are present in the BNST, although OX1R is more prominent (Marcus et al., 2001).

Cognition: orexins also project to areas involved in memory processing, mainly the PFC, hippocampus, and the medial and lateral septum. Several studies suggest a direct effect of orexin projections in these areas, as well as an indirect effect through the sleep-wake cycle regulation (Toor et al., 2021). The hippocampus presents a region-specific distribution of orexin receptors, thus expressing OX1R primarily in the dentate gyrus and CA1, and OX2R in CA3. The PFC mainly expresses OX1R, whereas the medial and lateral septum abundantly express OX2R (Marcus et al., 2001; Elahdadi Salmani et al., 2022).

3. Orexins and sleep disorders

Sleep and arousal disorders are common in a variety of mental and physical illnesses. These disturbances impair quality of life, affect health, and confer a significant economic burden to society (Huyett and Bhattacharyya, 2021). The most widely prescribed hypnotic agents are those which potentiate the activity of $GABA_A$ receptors, including benzodiazepines. However, these drugs are associated with important side effects and can lead to dependence. Considering these limitations, new approaches to improve sleep and modulate arousal are needed. As mentioned in section 2.2, orexin neurons project to different brain regions known to promote wakefulness and arousal, including the LC noradrenergic, raphe nuclei serotonergic, tuberomammillary nucleus

histaminergic, and basal forebrain cholinergic neurons (Li and de Lecea, 2020). These brain areas contain high density of orexin receptors although OX1R predominates in the LC while OX2R is mainly expressed in the tuberomammillary nucleus (Marcus et al., 2001). The role of orexins in the regulation of the sleep and wakefulness states was promptly established after the discovery that prepro-orexin or OX2R deficiencies caused narcolepsy in mice (Chemelli et al., 1999) and dogs (Lin et al., 1999), respectively. Subsequent experiments showed a loss of orexin neurons in postmortem brains of narcoleptic patients (Peyron et al., 2000; Thannickal et al., 2000) and reduced orexin concentrations in the cerebrospinal fluid (CSF) of people with narcolepsy (Nishino et al., 2000). In agreement with these studies, acute icv administration of OXA maintained wakefulness, suppressed sleep, and inhibited cataplectic attacks in a murine model of narcolepsy (Mieda et al., 2004). Moreover, icv infusion of this neuropeptide in rodents increased the duration of wakefulness significantly in a dose-dependent manner (Mieda et al., 2011), while administration of the OX2R antagonist MK1064 promoted non-rapid eye movement (NREM) and REM sleep across different species (Gotter et al., 2016). Optogenetic activation of orexin neurons also increased the probability of transition to wakefulness from either slow wave sleep or REM sleep (Adamantidis et al., 2007).

Direct infusion of OXA into the nuclei that receive projections from orexin neurons including the LC (Bourgin et al., 2000), the tuberomammillary nucleus (Huang et al., 2001) or the basal forebrain (Thakkar et al., 2001) has also been reported to increase the duration of wakefulness and suppressed REM sleep. These results were congruent with different electrophysiological experiments showing strong excitatory effects of orexins of wake-promoting systems such as serotonergic (Brown et al., 2001, 2002), cholinergic (Eggermann et al., 2001; Burlet et al., 2002) and histaminergic (Eriksson et al., 2001). On the other hand, orexin neurons also receive projections from some nuclei involved in sleep-wake regulation. For example, "sleep-active" neurons of the preoptic area of the hypothalamus contain the inhibitory neurotransmitter GABA and densely project to orexin neurons (Sakurai et al., 2005). Optogenetic stimulation of preoptic area fibers resulted in rapid inhibition of orexin neurons (Saito et al., 2013). On the contrary, orexin neurons are also innervated by cholinergic neurons in the basal forebrain, which have positive influence on wakefulness. Overall, orexin neurons are inhibited by sleep-promoting neurons and activated by wake-promoting neurons (Shen et al., 2022).

The specific role played by orexin receptors in the regulation of sleep/wakefulness has been investigated in several studies. The effects of icv infusion of OXA on wakefulness and NREM sleep were significantly attenuated in both OX1R and OX2R knockout (KO) mice, with considerably larger attenuation in OX2R KO animals (Mieda et al., 2011). These results suggest that although the OX2R-mediated pathway has a pivotal role in the promotion of wakefulness, OX1R also plays additional roles in promoting arousal. In contrast, suppression of REM sleep by OXA administration was slightly and similarly attenuated in both OX1R and OX2R KO mice, suggesting a comparable contribution of the two receptors to REM sleep suppression (Mieda et al., 2011). Both OX2R and orexin KO mice showed similar degrees of disrupted wakefulness and were similarly affected with anomalous attacks of NREM sleep ("sleep attacks") (Willie et al., 2003). In contrast, OX2R KO mice were only mildly affected with cataplexy-like attacks of REM sleep, whereas orexin KO mice were severely affected (Willie et al., 2003). These data suggest that normal regulation of wakefulness and NREM sleep depends essentially on OX2R activation, while the profound dysregulation of REM sleep control emerges from a loss of function of both OX1R and OX2R (Mieda, 2017).

As a result of scientific research, orexin receptor antagonists were developed as sleep-promoting agents. The nonselective orexin receptor antagonist almorexant showed increased sleep efficiency with shorter sleep latency and wake time after sleep onset. However, clinical trials were discontinued in Phase III due to transient liver function abnormalities (Hoch et al., 2014; Roecker et al., 2016). Two selective OX2R

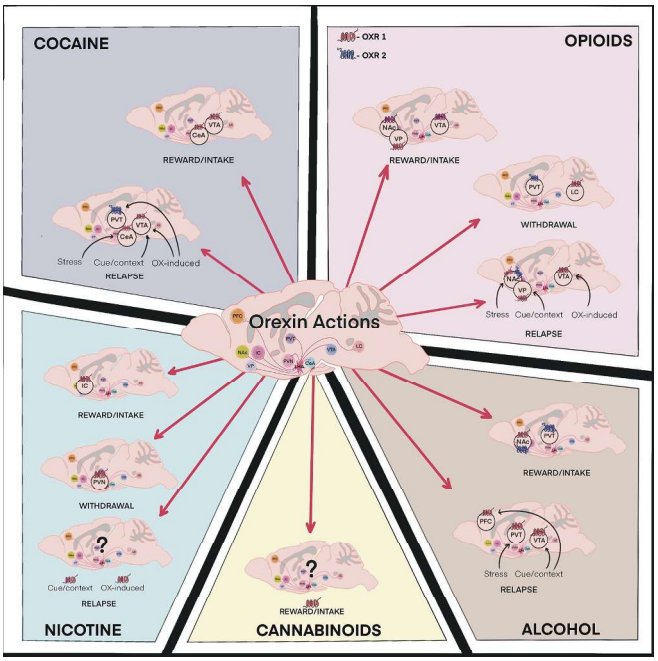

Fig. 2. Role of the orexin system in drug addiction. Orexinergic neurons located in the LHA modulate the addictive properties of diverse drugs of abuse through their widespread projections. Key brain regions and/or orexin receptor subtypes involved in each modulatory effect appear depicted when appropriate. CeA, central nucleus of the amygdala; IC, insular cortex; LC, locus coeruleus; LHA, lateral hypothalamic area; NAc, nucleus accumbens; PFC, prefrontal cortex; OX, orexins; PVN, paraventricular nucleus in the hypothalamus; PVT, paraventricular thalamus; VP, ventral pallidum; VTA, ventral tegmental area.

antagonists were also tested in humans, MK1064 and JNJ42847922. Both compounds demonstrated a dose-dependent increased in sleep efficiency (Bonaventure et al., 2015; Gotter et al., 2016). Suvorexant, a dual orexin receptor antagonist (DORA), was the first agent to be approved by the US Food and Drug Administration (FDA) for the treatment of insomnia in 2014. The increase in total sleep time was found to be due to increases in all sleep stages, although REM sleep was preferentially increased at higher doses. Common side effects were daytime somnolence and abnormal dreams (Herring et al., 2019). Lemborexant and daridorexant are DORAs also approved by the FDA for the treatment of insomnia disorder (Muehlan et al., 2020; Park et al., 2023). Unlike $GABA_A$ receptor modulators, DORAs promote NREM and REM sleep, do not disrupt sleep stage-specific quantitative electroencephalogram spectral profiles, and allow somnolence indistinct from normal sleep. The preservation of cognitive performance and the ability to arouse to salient stimuli after DORA administration suggest further advantages over historical therapies (Coleman et al., 2017).

As described above, given the destruction of orexin neurons observed in human cases of narcolepsy with cataplexy, orexin agonists could be developed to alleviate symptoms of this disease and treat excessive daytime sleepiness and/or hypersomnolence in a variety of other disorders (Black et al., 2017). Currently, these pathologies are mainly treated with systemic psychostimulants like modafinil or dexamphetamine, which produce severe side effects such as arrhythmias, high blood pressure, insomnia, and weight loss (Takenoshita and Nishino, 2020). An interesting strategy for these disorders is the orexin replacement therapy (Takenoshita et al., 2018). In human studies, OXA has been intranasal administered to reverse orexin neurons deficiency, thus inducing an arousal state (Weinhold et al., 2014). However, these therapies have not demonstrated efficacy, most likely due to insufficient brain exposure. Other administration routes already studied in animal models of narcolepsy, such as intrathecal injection, may be a viable option which requires further investigation in humans. On the other

hand, non-peptide low molecular weight and brain penetrant OX2R agonists are appealing due to the main role of OX2R in wake-promoting states. In this sense, the selective and brain-penetrant OX2R agonist danavorexton (TAK-925) was found to increase wakefulness in wild-type mice (Yukitake et al., 2019), in a mouse model of narcolepsy type 1 (Ishikawa et al., 2022), and in human patients with narcolepsy (Evans et al., 2022).

4. Orexins and addictive disorders

Drug addiction is a chronic brain condition characterized by compulsive drug seeking and drug taking despite its detrimental consequences, appearance of a negative affective state when drug access is discontinued, and relapse to seek the drug (Koob and Le Moal, 2008). During the last two decades, a growing amount of research has addressed the contribution of the orexin system to addictive-associated behaviors triggered by the most commonly consumed drugs of abuse, including cocaine, alcohol, opioids, nicotine and cannabinoids. This section summarizes the most relevant findings regarding each of these addictive drugs.

4.1. Cocaine

A considerable body of evidence demonstrate that orexins facilitate both cocaine-taking and cocaine-seeking behavior (Fig. 2). However, orexin transmission is not necessary for the primary rewarding properties of cocaine; instead, orexin peptides, mainly through OX1R signaling, become crucial specifically under highly salient and motivational conditions that require considerable effort to obtain the drug (Matzeu and Martin-Fardon, 2022). Thus, systemic OX1R blockade had no effect in cocaine-conditioned place preference (Sharf et al., 2010), or in cocaine self-administration under a low fixed-ratio schedule (FR) of reinforcement (Smith et al., 2009; España et al., 2010, 2011; Hollander et al., 2012; Zhou et al., 2012). Cocaine self-administration remained unaffected also by OXA icv administration (Boutrel et al., 2005). In contrast, OX1R antagonism reduced operant responding for cocaine in discrete trials with limited infusions per hour (España et al., 2010), under a progressive-ratio schedule (PR) of reinforcement (Borgland et al., 2009; Brodnik et al., 2015; Prince et al., 2015), in protocols with extended access to cocaine (Schmeichel et al., 2017), and in rats that displayed an addicted-like phenotype (James et al., 2019). Similar results have been obtained in rats where orexin expression was knocked down; these animals displayed lower operant responding for cocaine under PR and when given extended access to the drug (Schmeichel et al., 2018), confirming the relevance of orexin transmission in establishing and maintaining cocaine intake under highly demanding conditions or when cocaine access schedule promotes high motivation for the drug.

These results may be explained because orexin transmission modulates the effects of cocaine in mesolimbic dopaminergic transmission. Infusion of OXA directly into the VTA increased responding for cocaine in discrete trials and under PR of reinforcement but not under an FR (España et al., 2011), suggesting that orexin transmission to the VTA enhances the reinforcing efficacy and the motivational properties of cocaine under highly demanding conditions. This effect was mediated by OX1R (Muschamp et al., 2014). Consistently, intra-VTA infusion of OXA enhanced the raise of dopamine levels in the NAc induced by cocaine administration, whereas OX1R antagonism, but not OX2R blockade, caused the opposite effect (España et al., 2011, 2010; Prince et al., 2015). OX1R signaling within the central nucleus of the amygdala (CeA) is also crucial to control cocaine intake, since intra-CeA infusion of an OX1R antagonist reduced cocaine self-administration in rats under extended access conditions (Schmeichel et al., 2017).

Orexins are also key characters in the reinstatement of cocaine-seeking behavior after it has been extinguished or after drug abstinence. Central OXA infusion led to reinstatement of cocaine seeking (Boutrel et al., 2005; Wang et al., 2009). This effect was mediated by corticotropin releasing factor (CRF), suggesting a link between stress and orexins to modulate this behavioral response (Boutrel et al., 2005). Consistently, systemic injection of the OX1R antagonist SB334867 prevented stress-induced reinstatement of cocaine-seeking (Boutrel et al., 2005; Zhou et al., 2012), pointing to OX1R as a pivotal driver of drug-seeking behavior through stress-dependent mechanisms. OX1R blockade, but not OX2R antagonism, also reversed conditioned reinstatement of cocaine-seeking triggered by drug-associated cues (Smith et al., 2009; Zhou et al., 2012; Martin-Fardon and Weiss, 2014b) or cocaine-related context following either extinction or abstinence (Smith et al., 2010), but did not affect reinstatement elicited by a priming injection of the drug (Zhou et al., 2012). Taken together, these observations point to OX1R signaling as a key factor for reinstatement of cocaine-seeking induced either by stress or by drug-associated cues or contexts.

The VTA is one of the key regions leading the role of orexins in cocaine-seeking reinstatement, since direct infusion of OXA into this brain area reinstated cocaine seeking upon extinction, an effect dependent on OX1R but not on OX2R (Wang et al., 2009). Local OX1R antagonism in the VTA also attenuated cue-induced reinstatement of cocaine seeking (James et al., 2011), further supporting the role of OX1R signaling in the VTA as a cocaine-seeking promoter. The PVT constitutes another crucial orexinergic target, since direct infusion of OXA into the PVT also reinstated cocaine seeking upon extinction (Matzeu et al., 2016). In contrast to observations in the VTA, however, this priming effect of OXA was completely reversed by a concomitant injection of the OX2R antagonist TCSOX229 (Matzeu et al., 2016), but not by OX1R blockade (James et al., 2011). Interestingly, prolonged cocaine consumption increased OX2R immunoreactivity within the PVT at 2–3 weeks of abstinence and returned to basal levels at 5 weeks after the last cocaine exposure (Matzeu and Martin-Fardon, 2021), further suggesting that modulation of cocaine seeking by orexin transmission is mediated by OX2R in the PVT, and not by OX1R. Finally, stress-induced reinstatement of cocaine seeking was attenuated by previous infusion of the OX1R antagonist SB334867 into the CeA (Schmeichel et al., 2017). Altogether, these findings depict a brain region-dependent contribution of OX1R or OX2R as drivers of cocaine-seeking behavior.

4.2. Opioids

Several reports demonstrate that orexin transmission results crucial for addictive-like properties of opioid compounds (Fig. 2). Mice lacking the prepro-orexin gene do not express morphine-conditioned place preference and display abolished morphine-induced dopamine release in the NAc (Narita et al., 2006). This result, together with increased activation of VTA-projecting orexin neurons in rats exhibiting consistent place preference conditioning by morphine (Harris et al., 2005; Richardson and Aston-Jones, 2012), suggested that orexins contribute to the rewarding properties of morphine through a dopamine-dependent mechanism. Thus, systemic, intra-VTA or intra-NAc blockade of OX1R attenuated the expression of morphine-induced place preference (Harris et al., 2005; Narita et al., 2006; Sharf et al., 2010), pointing to OX1R expressed within the mesolimbic system as a key responsible for these findings. In addition, systemic administration of the OX1R antagonist SB334867 decreases operant self-administration of diverse opioid compounds in rodents, including heroin (Smith & Aston-Jones, 2012), oxycodone (Matzeu and Martin-Fardon, 2020a), fentanyl (Fragale et al., 2019) and remifentanil (Porter-Stransky et al., 2017; Mohammadkhani et al., 2019, 2020). Interestingly, SB334867 local injection into the ventral pallidum replicated the decrease observed in remifentanil self-administration after systemic OX1R blockade. On the other hand, systemic administration of the OX2R antagonist NBI80713 dose-dependently decreased heroin self-administration in rats that were given extended access to the drug (Schmeichel et al., 2015). However, oxycodone self-administration under the same procedural conditions remained unaltered after the pretreatment with another OX2R

antagonist, TCSOX229 (Matzeu and Martin-Fardon, 2020a). Differences in pharmacokinetic and pharmacodynamic profiles of these OX2R antagonists may account for these apparently contradictory results.

A growing body of evidence points to orexin transmission as a leading character in relapse to opioid seeking. OXA infusion into the VTA reinstated an extinguished morphine place preference in an OX1R-dependent manner (Harris et al., 2005). In agreement, the OX1R antagonist SB334867 decreased reinstatement of heroin self-administration elicited by discrete cues, but not by a priming injection of the drug (Smith and Aston-Jones, 2012). Consistently, OX1R blockade also prevented cue or context-induced reinstatement of oxycodone seeking (Matzeu and Martin-Fardon, 2020a), remifentanil seeking (Porter-Stransky et al., 2017) and fentanyl seeking (Fragale et al., 2019). OX1R signaling in the ventral pallidum, besides contributing to remifentanil reinforcement, also appears to drive cue-induced reinstatement of remifentanil-seeking behavior (Mohammadkhani et al., 2019, 2020). In contrast, OX2R might be noncritical for opioid relapse, since the OX2R antagonist TCSOX229 did not prevent conditioned reinstatement of oxycodone-seeking behavior (Matzeu and Martin-Fardon, 2020a). However, local blockade of either OX1R or OX2R in the NAc decreased stress-induced reinstatement of conditioned place preference for morphine, but neither of the orexin antagonists prevented reinstatement of morphine-preference elicited by a priming injection of the drug (Qi et al., 2013).

The orexin system constitutes also a pharmacological target to avoid somatic and negative affective symptoms of morphine withdrawal. Naltrexone- or naloxone-precipitated morphine withdrawal induces activation of orexin neurons (Georgescu et al., 2003; Sharf et al., 2008; Laorden et al., 2012) and both precipitated and spontaneous withdrawal increase orexin mRNA levels in the LHA (Zhou et al., 2006; Laorden et al., 2012). Prepro-orexin KO mice display attenuated somatic signs of morphine withdrawal induced by naloxone administration (Georgescu et al., 2003). OX1R signaling, particularly within the LC, is required for the somatic expression of morphine withdrawal (Sharf et al., 2008; Azizi et al., 2010; Laorden et al., 2012), whereas OX2R within the PVT contributes to the negative affective component of morphine withdrawal (Li et al., 2011).

4.3. Alcohol

A considerable body of evidence supports the contribution of the orexin system to the addictive properties of alcohol (Fig. 2). Of note, studies with this regard appear sometimes controversial, since the role of orexins in the hedonic- and metabolic-associated appetite for other orally consumed natural rewards entails a relevant confounding factor. OX1R signaling has robustly proven, however, to control the rewarding and motivational properties of alcohol. The administration of the SB334867 antagonist reduced alcohol intake and operant responding for alcohol in genetically alcohol-preferring rat strains, under FR or PR of reinforcement (Lawrence et al., 2006; Jupp et al., 2011). Similarly, OX1R blockade attenuated alcohol preference on a two-bottle free-choice paradigm (Moorman and Aston-Jones, 2009) and alcohol self-administration (Richards et al., 2008; Moorman et al., 2017) in outbred wild-type rats trained to consume alcohol. OX1R antagonism also reduced alcohol consumption in mice models characterized by high impulsivity (i.e., binge-like alcohol intake) (Olney et al., 2015), compulsivity (i.e., alcohol consumption even in presence of the bittering quinine) (Lei et al., 2016) and dependence (Lopez et al., 2016) for alcohol. Importantly, OX1R antagonist doses able to decrease alcohol intake had no effect in consumption of other natural rewards (i.e., sucrose, saccharine) (Richards et al., 2008; Olney et al., 2015; Lopez et al., 2016). Other studies, however, did not observe a decrease in alcohol-induced place preference in mice (Voorhees and Cunningham, 2011) or alcohol self-administration in rats (Shoblock et al., 2011) after OX1R blockade, suggesting that orexinergic influence in alcohol intake and motivation for the drug emerges under specific experimental protocols modelling particular components of alcohol use and abuse. Alcohol-induced reward also requires OX2R signaling, since systemic administration of the OX2R antagonists JNJ10397049 and LSN2424100 respectively reduced alcohol self-administration (Shoblock et al., 2011) and attenuated motivation for alcohol intake in alcohol-preferring rats (Anderson et al., 2014). When centrally administered, also the OX2R antagonist TCSOX229 was able to attenuate alcohol self-administration (Brown et al., 2013), confirming the role of OX2R in alcohol intake.

The NAc is one of the key orexinergic targets involved in alcohol-induced reward and motivation, since an OX1R antagonist (injected in the shell) (Lei et al., 2019; Kwok et al., 2021) and an OX2R antagonist (injected in the core) (Brown et al., 2013) are able to reduce alcohol drinking. In contrast, alcohol consumption remained unaffected by the blockade of OX2R in the VTA and CeA (Olney et al., 2017). Infusion of OXA or OXB in the PVT increased alcohol intake in an intermittent access procedure, an effect that was reversed by OX2R but not OX1R blockade (Barson et al., 2015, 2017). These findings further support the role of orexin receptors in voluntary alcohol consumption while providing valuable clues on the key brain regions involved in this modulation.

Several studies have demonstrated the strong contribution of the orexin system to alcohol-seeking and relapse. Orexinergic neurons are recruited under context- and cue-induced alcohol seeking (Hamlin et al., 2007; Dayas et al., 2008; Moorman et al., 2016). OX1R blockade, but not OX2R antagonism, prevented cue-induced reinstatement of alcohol-seeking (Lawrence et al., 2006; Brown et al., 2013; Martin-Fardon and Weiss, 2014a; Moorman et al., 2017). OX1R signaling within the VTA, the mPFC and the hypothalamus, but not in the BNST, crucially drive this behavioral response, since local infusion of SB334867 in these brain regions also reduced alcohol seeking triggered by cue presentation or drug-associated context (Brown et al., 2016; Campbell et al., 2020). Systemic SB334867 administration also inhibited stress-induced reinstatement (Richards et al., 2008), although it prevented stress-induced reinstatement of sucrose seeking as well. Similarly, local infusion of a DORA within the PVT prevented stress-induced reinstatement of alcohol-seeking selectively in alcohol-dependent rats, but also attenuated seeking of sweetened condensed milk in rats dependent for this natural reward (Matzeu and Martin-Fardon, 2020b). Overall, orexin transmission, particularly through OX1R, is required for reinstatement of alcohol-seeking induced by cue/context, and probably by other triggers, although the neural circuit involved might be shared with seeking of natural rewards.

4.4. Nicotine

The contribution of orexin transmission to the addictive properties of nicotine has been less explored than to addiction to other abuse drugs (Fig. 2). A common trait that nicotine shares with other abuse substances is the activation of orexin neurons upon acute nicotine injections (Pasumarthi et al., 2006). Chronic nicotine administration also increased the expression levels of orexin peptides and receptors in the rat hypothalamus (Kane et al., 2000), suggesting that nicotine induces neuroadaptations within the orexin system. Orexin transmission also promotes nicotine reinforcement and motivation to obtain the drug, since systemic OX1R antagonism attenuated nicotine self-administration under both FR and PR of reinforcement in rats (Hollander et al., 2008; LeSage et al., 2010). Conversely, blockade of OX2R signaling had no effect on these behavioral responses, indicating that OX2R is unnecessary for nicotine (Uslaner et al., 2014). A key clue for identification of particular brain regions involved in orexin control of nicotine intake came from the clinics, where it has been observed that stroke-associated damage to the insular cortex in tobacco-smoker subjects led to spontaneous discontinuation of the smoking habit (Naqvi et al., 2007). In accordance, infusion of the OX1R antagonist SB334867 into the insular cortex reduced nicotine self-administration in rats (Hollander et al., 2008), proposing OX1R signaling in the insular cortex

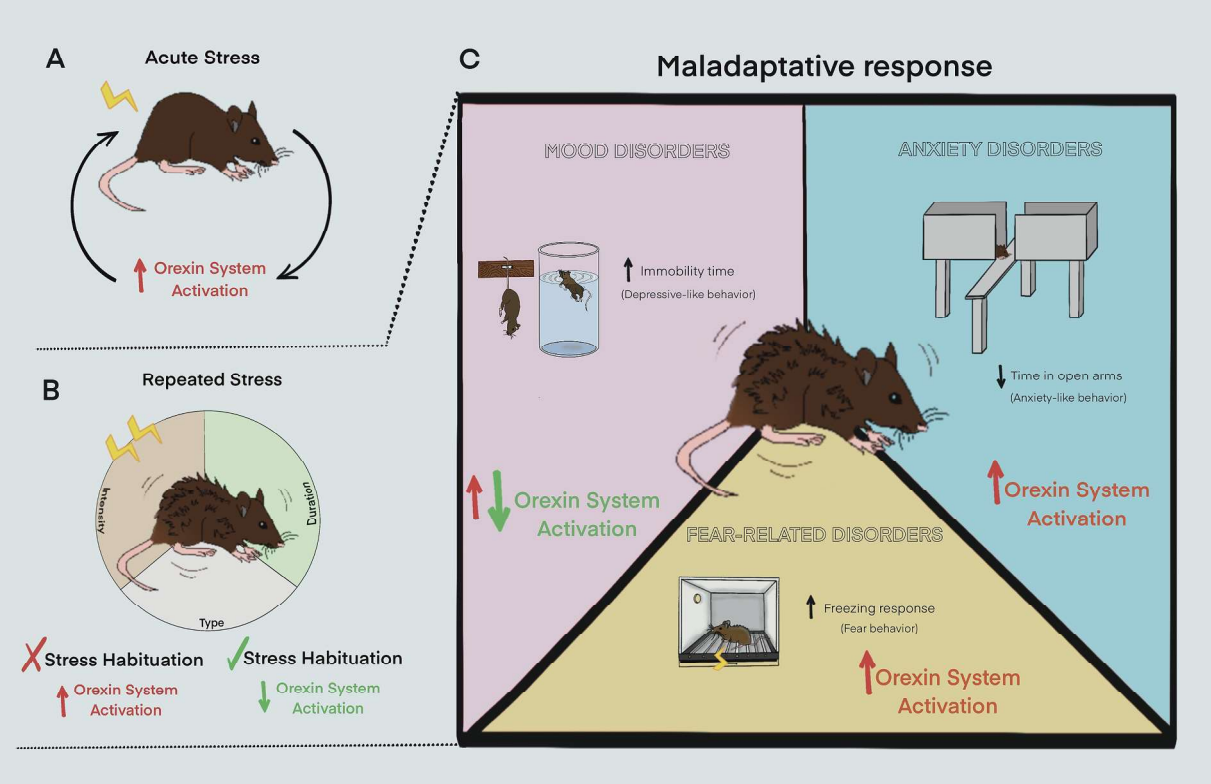

Fig. 3. Role of the orexin system in acute and repeated stress: pathological consequences. (A) Acute stress and activation of the orexin system present a positive correlation, (B) whereas repeated stress increases or decreases the activity of the orexin system depending mainly on the habituation to the stressor stimuli. (C) Chronic stress might induce stress-related disorders, such as mood, anxiety, and fear-related disorders. Mood disorders are mainly assessed by the tail suspension and the forced swimming tests. Although both hyper- and hypo-activation of the orexin system are described in this disorder, most of the studies support a reduced activity. Anxiety and fear-related disorders are mainly evaluated by the elevated plus maze test and the fear conditioning paradigm, respectively. Both are mainly related with an increase in the activity of the orexin system.

as a crucial driver of nicotine intake.

Orexin peptides are key characters in relapse to nicotine-seeking behavior. Thus, central infusion of OXA reinstates a previously extinguished nicotine self-administration in mice in a OX1R-dependent manner (Plaza-Zabala et al., 2010). Interestingly, and unlike orexin-induced cocaine reinstatement, nicotine seeking primed by OXA was CRF independent (Plaza-Zabala et al., 2010). In addition, pretreatment with the OX1R antagonist SB334867 but not the OX2R antagonist TCSOX229 decreased cue-induced reinstatement of nicotine seeking (Plaza-Zabala et al., 2013). In contrast, this behavioral response was effectively prevented by another OX2R antagonist, 2-SORA 18 (Uslaner et al., 2014). Different bioavailability and distribution of these OX2R antagonists is possibly responsible for these divergent results, as observed in other experimental settings (e.g., opioid self-administration). Additional research is thus required to clarify the specific role of each orexin receptor in relapse to nicotine seeking.

Finally, orexin transmission also plays a relevant role in the expression of nicotine withdrawal. Thus, systemic blockade of OX1R by SB334867, but not of OX2R by TCSOX229, diminished the somatic signs of mecamylamine-precipitated nicotine withdrawal in mice, an effect also observed in prepro-orexin KO animals (Plaza-Zabala et al., 2012). In addition, nicotine withdrawal precipitation induced the activation of the PVN of the hypotlamaus. Local infusion of SB334867 into this brain area reversed PVN activation upon nicotine withdrawal precipitation and decreased its somatic manifestations (Plaza-Zabala et al., 2012), confirming that OX1R signaling in the PVN is required for expression of nicotine withdrawal.

4.5. Cannabinoids

Evidence pointing to a potential role of orexins in the addictive properties of cannabinoids is still scarce (Fig. 2). However, strong reasons suggest that it might be the case; first, as mentioned, orexinergic dysregulation is a prevalent factor across addiction to many other drugs of abuse. Second, a growing body of evidence supports the existence of a reciprocal interaction between orexinergic and endocannabinoid systems at biochemical and functional levels (Berrendero et al., 2018), as observed in antinociception and in reward seeking. Indeed, exposure to cannabinoids induces certain neuroadaptations in the orexinergic system. Mice that self-administer the synthetic cannabinoid WIN55,212–2 showed increased activation of orexin neurons within the LHA, an effect not observed in those animals passively receiving the drug (Flores et al., 2014a). This suggests that orexinergic cells become active during operant seeking for the reinforcing effects of this cannabinoid, but not to its pharmacological effects. In contrast, Δ^9-tetrahydrocannabinol (THC)-smokers show decreased orexin expression in peripheral blood cells when compared to cigarette-smokers or non-smokers (Rotter et al., 2012). Although these data might be more related to peripheral actions of THC rather than to the central effects involved in dependence, it remains unclear which neuroadaptations undergo orexin neurons due to cannabinoid exposure. On the other side, systemic administration of the OX1R antagonist SB334867, but not the OX2R antagonist TCSOX229, diminished the reinforcing and motivational properties of the synthetic cannabinoid in WIN55,212–2-seeking mice. Additionally, OX1R deficient mice displayed lower THC-induced dopamine release in the NAc shell (Flores et al., 2014a), suggesting that OX1R modulation of the rewarding properties of cannabinoids could be dopamine-mediated.

In summary, a large body of evidence supports the potential benefits

of targeting the orexin system in the clinical management of drug addiction. In fact, the National Institute on Drug Abuse (NIDA) has recognized orexin receptor antagonists and/or negative allosteric modulators among their list of priority targets for new medications to face the opioid crisis (Rasmussen et al., 2019). The regulatory approval of the dual orexin receptor antagonist suvorexant for clinical use in insomnia has paved the path to launch several ongoing clinical trials to assess its efficacy in treating addiction to cocaine (NCT03937986, NCT02785406), opioids (NCT04262193, NCT04287062, NCT05145764), alcohol (NCT04229095, NCT03897062, NCT05656534), nicotine (NCT03999099, NCT05630781) or stimulant/opioid co-use (NCT05546515). Promising results have been recently reported in opioid users, where suvorexant ameliorated sleep disturbances and opioid withdrawal and craving (Huhn et al., 2022). Non-treatment seeking cocaine users also benefited from improved sleep and reduced cocaine craving (Suchting et al., 2020), although suvorexant did not diminished the use of cocaine (Suchting et al., 2020) or its reinforcing properties (Stoops et al., 2022). Forthcoming results will be key to unravel which specific symptoms or disease stages may benefit most from orexin antagonism.

5. Orexins and stress-related disorders

Contrary to the general perception, stress is an adaptative and physiological response generated to overcome stressful stimuli, which threaten our survival, such as social or environmental factors. However, chronic stress may induce a maladaptive response in the CNS by causing alterations in neurogenesis, synapse density, dendritic architecture, and gene expression, thus promoting vulnerability to, or potentiating the symptoms of, almost all mental illnesses (McEwen et al., 2015). In contrast to the clinical view of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), pre-clinical research clusters mental diseases by considering their etiopathology. Thus, stress-related disorders include mood (i.e., major depressive and bipolar disorders), anxiety, and fear-related disorders (i.e., posttraumatic stress disorder (PTSD), panic, and phobias) (Smoller, 2016; Barbano et al., 2019). In this sense, stress precedes the onset of anxiety (Juruena et al., 2020), and a large percentage of depressive patients experienced previous episodes of chronic stress with increased levels of ACTH and cortisol (Bhagwagar et al., 2005; Siegrist et al., 2012). Hence, stress is one such "lowest common denominator" for these psychiatric disorders, as detailed below.

The orexin system is a major modulator of the stress response. Accordingly, the most relevant stress-sensitive brain areas receive dense hypothalamic projections from orexin neurons (Peyron et al., 1998). Clinical and preclinical studies clearly differentiate between acute and repeated stress, given the pathological consequences resulting from the second type. Several studies have described the involvement of the orexin system in acute stress reactions, whereas less is known about the role of orexins in chronic stress (Fig. 3).

5.1. Acute stress

As mentioned before, the acute stress response is a spontaneous and natural reaction against potential threats and unpredictable events. It prepares the body to cope in a survival situation by increasing arousal through the hypothalamic pituitary adrenal (HPA) axis activation, among other mechanisms (Sargin, 2019). Central administration of orexins induces an acute stress reaction which produces grooming, burrowing and face washing in rats (Ida et al., 1999). Accordingly, orexin deficient mice presented the opposite effect by reducing the activity in a resident-intruder paradigm, thus indicating a diminished behavioral response to stress (Kayaba et al., 2003). An interesting study recently published by Yaeger and co-workers indicates that both antagonism or genetic knockdown of OX1R in the basolateral amygdala (BLA) switches the behavioral expression in the Stress Alternatives Model. In this test, smaller mice are placed with a larger novel aggressor and given a chance to exit through escape tunnels. Blockade or down-regulation of OX1R induced a stress-resilient response (i.e. escape), in comparison to the control mice that presented a stress-sensitive response (i.e. stay) (Yaeger et al., 2022). Reciprocally, acute stress augments orexin neuron activity. In this sense, a single restraint in rats increased the percentage of active orexin neurons marked with cFos, an indicator of neuronal activity (Grafe et al., 2017b) (Fig. 3).

The molecular basis underlying these alterations mainly relies on the HPA axis and the sympathetic nervous system (SNS), which are essential components to initiate stress-coping mechanisms. On the one hand, orexins favor HPA axis response to acute stress at all levels, as well as HPA activation promotes orexin activity. For example, icv infusion of orexins activates CRF-expressing neurons and increases downstream HPA hormones ACTH and corticosterone (Kuru et al., 2000; Al-Barazanji et al., 2001). Increased levels of ACTH are mediated by OX1R and OX2R in the pituitary (Date et al., 2000). Orexins also act peripherally on the adrenal glands, thus stimulating glucocorticoid secretion (Mazzocchi et al., 2001). In the opposite direction, activation of the HPA axis by CRF administration increases orexin neuron activity, as revealed by electrophysiological data of mice slices (Winsky-Sommerer et al., 2004).

On the other hand, SNS activation is acutely induced by orexins. Sympathetic activity signs, such as blood pressure, heart rate, and renal sympathetic nerve activity are significantly increased by orexin central administration in rats (Shirasaka et al., 1999). Accordingly, orexin KO mice exhibited attenuated heart rate and blood pressure in the resident-intruder test (Kayaba et al., 2003). Diverse studies point the medulla and the nucleus of the solitary tract as the main orexin targets to exert the activation of the SNS in response to acute stress (de Oliveira et al., 2003; Huang et al., 2010).

5.2. Repeated stress

The role of the orexin system on the modulation of repeated stress response remains to be clearly defined (Fig. 3). While acute stress positively and reciprocally correlates with orexin activation, the role of the orexin system in repeated stress depends on several factors such as the intensity, type, and duration of the stressor. Also, the ability to habituate to the stressful stimuli is a key element to determine the activity of the orexin system. For example, repeated restraint in male rats for five days (30 min per day) decreased both OXA levels in the CSF and orexin neuronal activation (Grafe et al., 2017b). Conversely, 14 days of repeated restraint (2 h per day) in male mice produced the opposite effect: an increase of orexin mRNA transcripts in the BLA (Kim et al., 2015). Taking this comparison into account, a stronger-intensity and longer-duration stressor may probably cause a lack of habituation which would explain the increased orexin activity. Furthermore, the brain areas analyzed are different in each study, thus adding an additional variability given the different role exerted by the BLA in comparison with the LHA. An interesting study performed in male rats that underwent repeated forced swim stress revealed that OX1R in the posterior PVT is critical for adaptation to repeated stress (Heydendael et al., 2011). However, other sites expressing orexin receptors may also be involved in the habituation to chronic stress. In another study, unpredictable chronic mild stress (UCMS; different stressors randomly presented) in male mice produced a significant activation of orexin neurons in the dorsomedial and perifornical hypothalamic area (Nollet et al., 2011). Therefore, variations in the type of stressor prevent habituation which, in turn, increases orexin activity. In conclusion, the intensity, duration, and type of stressor stimuli are critical parameters to induce or prevent habituation in a repeated stress paradigm, which seems to negatively correlate with orexin activity.

A dysregulation of the orexin system has been observed in diverse neuropsychiatric diseases, including mood, anxiety, and fear-related disorders. Hence, the orexin system may become a potential therapeutic target to treat these stress-related mental illnesses (Fig. 3).

5.2.1. Mood disorders

According to the sixth chapter of the International Classification of Diseases - version 11 (ICD-11), which describes "Mental, behavioral or neurodevelopmental disorders", mood disorders, also known as affective disorders, mainly group bipolar and depressive diseases (Kogan et al., 2021). Although no animal model developed to date fully mimic the human complexity of bipolar or major depressive disorder (MDD), endophenotype-based modelling is an effective and promising tool to better understand the neurobiology of mood disorders. In this sense, the Wistar-Kyoto rat strain recapitulates key hormonal and behavioral features that resemble those observed in depressive patients (Will et al., 2003). These animals present deficiencies in the orexin system in comparison with the control Wistar rat strain, including reduced levels of the prepro-orexin mRNA, lower OXA immunoreactivity in diverse brain regions, and lower number of hypothalamic orexin neurons (Taheri et al., 2001; Allard et al., 2004). However, epigenetic factors (mainly stress) rather than genetic alterations are the most frequent cause of mood disorders. For that reason, chronic stress is commonly used to reach a depressive-like behavior in experimental animals. Rats exposed to the resident-intruder social defeat paradigm after house isolation presented several anhedonia-like symptoms and displayed reduced levels of both OXA and OXB peptides in the hypothalamus, mPFC, and VTA (Nocjar et al., 2012). Another study revealed that OXA administration exerted antidepressant-like effects in mice that underwent chronic social defeat stress. (Chung et al., 2014). Other potential etiologic stressors that induce a depressive state are helplessness and hopelessness (Abramson et al., 1989). By administering uncontrollable and inescapable foot or tail shocks, some rats display a learned helplessness behavior (i.e., depressive-like behavior), as they accept shocks even when they have the opportunity to avoid them (Seligman and Beagley, 1975; Vollmayr and Gass, 2013). These animals present significantly lower OXA levels in the brain, less OXA-expressing neurons, and less OXA-expressing neurons activation. Surprisingly, OXB-expressing neurons and OXB-expressing neurons activation were increased in learned helplessness rats, thus suggesting an opposite role of OXA and OXB in this animal model of depression (Hsu and Wang, 2021). Another frequently used stressor to develop a depressive-like behavior is early life trauma. A group of male and female rats was subjected to maternal separation stress, one type of early life trauma. In adulthood, these animals presented behavioral changes consistent with a depressive-like phenotype, by reducing exploration in the open field test, without affecting elevated plus maze (EPM) behavior. These rats were also exposed to restraint stress and the activity of orexin neurons was evaluated. Since restraint stress produces an activation of orexin neurons, this neuronal response was diminished in rats exposed to early life stress (James et al., 2014).

In contrast to the previously supported hypofunction of the orexin system in depressive-like behavior, other studies support the opposite idea. Hence, OX1R KO mice and pharmacological blockade with the OX1R antagonist SB334867 produced an antidepressant effect in the forced swim and tail suspension tests. Contrarily, OX2R KO mice exhibited an increased depressive-like behavior, in comparison with wild-type animals (Scott et al., 2011). A clearer result was obtained with the genetic model of depression Flinders Sensitive Line (Overstreet et al., 2005), which presents an augmented number of orexin neurons (Mikrouli et al., 2011). Hyperactivity of the orexin system has also been observed in non-genetic models of depression. For example, UCMS-induced depressive-like behavior in male mice caused increased orexin neuron activity. In the same study, chronic administration of the DORA almorexant promoted antidepressant-like effects in the tail suspension test (Nollet et al., 2011). Also, a mouse model of depression as a result of repeated restraint presented upregulated orexin mRNA in the BLA. Reciprocally, intra-BLA infusion of orexins produced a depressive-like behavior, whereas siRNA-mediated suppression of orexins in the same region blocked the depressive state (Kim et al., 2015).

In human studies, plasma OXA levels of both unipolar and bipolar depressive individuals are decreased (Ünler et al., 2022), as well as CSF levels of OXA in MDD suicidal patients (Brundin et al., 2007). Moreover, a clinical study performed with Japanese population presented decreased plasma OXA levels in bipolar individuals, while a clear trend was observed in MDD patients (Tsuchimine et al., 2019). On the contrary, a recent study has reported increased OXA plasma levels in MDD and bipolar patients (Li et al., 2021b), although a similar study with adolescents aged 12–18 years presented no differences between MDD and healthy controls (Akça et al., 2021). Seltorexant, a selective antagonist of OX2R, slightly reduced depressive symptoms only in a specific dose. Interestingly, long-term differences between placebo and seltorexant were significant in patients with severe insomnia, thus suggesting a sleep improvement which might indirectly affect the depressive state (Savitz et al., 2021).

Altogether, these findings indicate an involvement of the orexin system in the neurobiological mechanisms underlying mood disorders. However, dissimilarities in the results obtained suggest that variables are not homogeneous when analyzing the depressive-like phenotype. The stressor type, duration, intensity, and habituation might probably affect the depressive-like behavior and, in turn, the orexin system dysregulation. It would be also important to clarify the role of each component of the orexin system, since opposite roles have been observed between orexin peptides and receptors. Although many studies give a favorable consideration to the hypofunction of the orexin system in mood disorders, further and uniform research is needed to clearly elucidate this notion.

5.2.2. Anxiety disorders

Psychological, physiological, or pharmacological stressors are commonly used to induce an anxiety-like behavior, including those characterized by a pathological fear as explained in section 5.2.3. The first study directly linking orexins and anxiety appeared in 2005 by Suzuki et al. They observed an anxiety-like behavior in the EPM and light–dark tests after central administration of OXA in male mice and rats (Suzuki et al., 2005). Accordingly, optogenetic studies revealed that orexin cell activation reduced time spent in the interaction zone in a social interaction test (Heydendael et al., 2014), and increased the inactive time in the open field test (Bonnavion et al., 2015). Another study demonstrated that OX2R activation in the NAc shell mimicked the OXA-induced anxiogenic effect, whereas the infusion of the OX2R antagonist TCSOX229 produced an anxiolytic behavior in male rats (Li et al., 2021a). In the same vein, cat odor-induced anxiety in rats was attenuated by the OX1R antagonist SB334867. This anxiogenic effect induced an overactivation of some stress-related brain areas, such as the PVN and dorsal premammilary nucleus, which was reduced by OX1R blockade (Vanderhaven et al., 2015). By contrast, orexin-deficient mice presented increased anxiety in EPM, open field, light–dark and carnivore odor-induced avoidance tests (Khalil and Fendt, 2017), thus indicating that an imbalance on the orexin system by increased or decreased orexin levels might induce an anxiety-related phenotype.

Further research has shed light on the underlying mechanisms of orexin-induced anxiety. Hence, Palotai and colleagues reported that mice pretreated with the $GABA_A$ antagonist bicuculline, the nonselective α-adrenergic receptor antagonist phenoxybenzamine, or the β-adrenergic receptor antagonist propranolol, 30 min before the icv infusion of OXA, prevented the anxiogenic behavior induced by OXA in the EPM test. These results provide evidence that OXA causes an anxiety-like behavior through GABA-ergic, α- and β-adrenergic neurotransmissions (Palotai et al., 2014). Moreover, activation of orexin neurons by optogenetic stimulation led to an increased OX1R internalization and ERK phosphorylation in the PVT and LC, two stress-related areas heavily innervated by orexin neurons (Heydendael et al., 2014). A study previously mentioned by Bonnavion and colleagues also described an inhibitory mechanism of the orexin-induced stress response, mediated by leptin. This satiety hormone acts, partially, through a network of leptin-sensitive neurons in the LHA (Bonnavion et al., 2015).

A clinical investigation with adolescents aged 12–18 years reported higher serum OXA levels in the group of individuals with anxiety disorders, in comparison with healthy controls (Akça et al., 2020). As current therapies for anxiety disorders present a suboptimal efficacy (Gupta and Prabhavalkar, 2021), further research in the field of orexins might pave the road to novel and potent pharmacological treatments. In this regard, a recent study with humans has demonstrated a reduction in objective indicators of anticipatory anxiety, through the blockade of both orexin receptors with suvorexant (Gorka et al., 2022). Accordingly, the selective OX1R antagonist ACT-539313 diminished cortisol levels at the beginning of an anxiety- and panic-induction proof and presented a clear trend to reduce subjective anxiety scores (Kaufmann et al., 2021).

5.2.3. *Fear-related disorders*

Fear is an essential emotion for the organization of defensive behaviors to threat and, in turn, for survival. However, dysregulation of the underlying mechanisms might give rise to diseases associated with inappropriate retention of fear, such as PTSD, panic, and phobias. The main areas involved in the regulation of fear memories are the amygdala, hippocampus and mPFC. Additionally, this response requires the participation of other structures, such as the periaqueductal grey matter, BNST, LC and PVT. In rodents, aversive memory has been classically studied by Pavlovian fear conditioning and subsequent extinction. In this paradigm, the amygdala remains as the central regulator of aversive memories, the hippocampus is responsible for assembling the contextual cues and transmitting this information to the amygdala, and the mPFC is involved in both the formation of fear memories (mainly those associated with auditory cues) and fear extinction, by the prelimbic (dorsomedial PFC in humans) and infralimbic (ventromedial PFC in humans) portions of the mPFC, respectively. The orexin system has been reported to have a key role in the modulation of neural circuits implicated in the expression and extinction of fear memories (Flores et al., 2015).

Genetic mice models report a key role of OX1R in the modulation of fear. Hence, OX1R KO mice showed diminished freezing responses and reduced expression of zif268 (a marker of neuronal activation) in the lateral amygdala, in both cued and contextual fear-conditioning paradigms. On the other hand, OX2R KO mice presented reduced freezing behavior in a contextual fear test, whereas normal freezing was shown in the cued fear paradigm (Soya et al., 2013). In agreement, increased prepro-orexin mRNA levels were positively correlated with immobility time after footshock exposure in rats (Chen et al., 2014). Pharmacological experiments confirmed the involvement of OXR1 in fear regulation. OXR1 antagonism with SB334867 decreased freezing related to contextual fear while OX2R blockade with TCSOX229 had no effect (Wang et al., 2017). Intra-amygdala infusion of SB334867 also reduced fear memory acquisition (Salehabadi et al., 2020), suggesting an involvement of amygdalar OX1R in this effect. In addition, a role of OX1R in the LC in threat learning was revealed by pharmacological and optogenetic approaches. In this study, pharmacological blockade of OX1R in the LC impaired threat memory formation induced by an auditory stimulus. Moreover, optical stimulation of orexin fibers in the LC was sufficient to enhance this response (Sears et al., 2013). The participation of the circuit involving orexin, noradrenergic neurons in the LC and lateral amygdala neurons was corroborated by a later study by pharmacogenetic/optogenetic approaches (Soya et al., 2017).

Orexins also modulate the extinction of acquired aversive memory. The administration of the OX1R antagonist SB334867 facilitated fear extinction in mice in both contextual and cued tests, while icv infusion of OXA impaired this response (Flores et al., 2014b). In agreement, the activity of orexin neurons was negatively correlated with successful extinction of conditioned fear in rats (Sharko et al., 2017). Reactivity to CO_2 was significantly predictive of orexin activity in the LHA, and in turn high orexin activity was associated with poor extinction (Monfils et al., 2019). Impaired fear extinction induced by the overactivation of the orexin system has been recently associated with the endocannabinoid 2-AG and CB2 cannabinoid receptors located in the amygdala (Ten-Blanco et al., 2022). On the other hand, several studies measuring immediate-early gene expression conclude that hypoactivity of specific brain areas of the cortico-amygdala circuit is related to impaired fear extinction while complete extinction of conditioned fear is associated with increased immediate-early gene expression in these areas (Herry and Mons, 2004). Interestingly, the extinction-facilitating effects of SB334867 were related to increased activity of the infralimbic mPFC and BLA (Flores et al., 2014b). Moreover, SB334867 increased the activity of BLA neurons projecting to infralimbic mPFC during fear extinction (Flores et al., 2017), a circuit which is known to be recruited during this behavioral response (Senn et al., 2014).

In humans, several studies have also described a relationship between orexins and fear-related disorders. Individuals with narcolepsy, a condition associated with a loss of orexin neurons (Peyron et al., 2000), showed reduced amygdala activity and failed to acquire fear memory during aversive conditioning (Ponz et al., 2010). JNJ61393215, a novel selective OX1R antagonist, attenuated CO_2-induced panic-behavior in rats and humans (Salvadore et al., 2020). Patients with panic anxiety symptoms show elevated CSF orexin concentrations (Johnson et al., 2010). In contrast, combat veterans with PTSD presented reduced OXA plasma and CSF levels (Strawn et al., 2010). Such evidence has given rise to diverse clinical trials evaluating trauma-related disorders with suvorexant (NCT03642028, NCT02704754, NCT02849548).

Collectively, these data clearly manifest a positive correlation between orexin system activation and the severity of fear-related diseases. Since fear response is a complex physiological reaction that involves many players, the key role of the orexin system in fear-related disorders might open up more tractable avenues for developing new drugs for these ineffective-treated illnesses.

6. Orexins and eating disorders

Anorexia nervosa (AN), bulimia nervosa (BN), and binge eating disorder (BED) are serious psychiatric disorders with often chronic courses, multifactorial etiopathogeneses, and poorly understood biological maintenance factors (APA, 2013). Research aimed at identifying common elements of comorbidity has focused on potential alterations in the neurobiology of hunger and satiety by pointing to factors like anxiety, mood disturbances, impulsive and compulsive behavior.

Eating disorders reflect opposite pathological behaviors toward food such as “avoidance” and/or “addiction” similar to drug abuse. From this perspective, food and drug craving share loss of control over how much food is consumed, repeated unsuccessful attempts to abstain from food consumption, neuronal networks and neurochemical pathways (Trinko et al., 2007; Avena et al., 2008; Volkow et al., 2008). Moreover, prolonged binge eating, also defined as “food addiction”, has been well-established as a compulsive behavior in BN or BED, and has been observed in obese patients (APA, 2013). We review in this section evidence supporting the hypothesis that the orexin system is involved in compulsive eating, food-seeking behavior, and food craving associated with the failure of homeostatic control of food consumption (Pich and Melotto, 2014).

Given preclinical research demonstrating that orexins stimulate feeding and hedonic eating and their levels are altered in AN and normalize as patients recover (Janas-Kozik et al., 2011; Bronsky et al., 2011; Sauchelli et al., 2016), growing evidence support orexin implications in eating disorder psychopathology and treatment. In this regard, an unexpected link is emerging between orexin glucose sensing and rewarding goal-oriented behavior since glucose plasma levels inhibit both arousal- and reward-related function by reducing the electrical activity of orexin glucose-sensing neurons and promoting the onset of depression. In detail, it has been found that plasma glucose is able to inhibit orexin neurons by extracellular activation of two-pore domain K^+ channels, thereby inducing anxiolytic, rewarding, and soporific effects of sugar. On the opposite, low glucose plasma levels stimulate feeding and reward seeking (Burdakov et al., 2006).

Further data support the hypothesis that the orexin system subtends a mechanistic link between eating disorders, sleep dysregulation and anxiety in a cyclic manner. Evidence comes from different studies showing that corticostriatal projections, which mediate inhibitory control of motivated behavior by controlling impulsivity (Kalivas and Volkow, 2005; Baldo and Kelley, 2007), are selectively weakened in mice following acute (6 h) sleep deprivation (Liu et al., 2016). These changes are accompanied by increased sucrose consumption in rodents and reversed by optogenetic stimulation of corticostriatal projections.

Chronic palatable food exposure activates orexin neurons by enhancing orexin signaling to several different brain output areas in rodents. In mice exposed to a high-fat diet, changes in orexin neuronal activity has been found (Horvath and Gao, 2005) and different studies report increase of prepro-orexin mRNA levels in monkeys and rats exposed to a high-fat diet also during early life (Wortley et al., 2003; Beck et al., 2006; True et al., 2018). Accordingly, it has been observed an enhancement of orexin trafficking and release to the VTA and PVN nuclei regulating reward and appetite, respectively (Cristino et al., 2013; Tunisi et al., 2021). Altogether, these data show that chronic or intermittent access to palatable foods (high fat, high sugar or a combination), by causing enhancement of orexin signaling to reward brain areas, promotes a vicious circle by increasing BN or BED via compensatory behaviors (eating to stay awake) (Mehr et al., 2021).

Obesity and binge eating are more prevalent among women than men, and it is important to compare the effects of pleasurable versus physiological food consumption, and their underlying neural mechanisms, in both genders. Results from a study investigating the consumption of high-sugar foods in male and female rats when they were either hungry or satiated indicated that, during multiple tests, female rats consistently consumed similar amounts of palatable food regardless of their hunger/satiety state, whereas male rats adjusted their consumption accordingly. This difference was only observed in palatable food consumption, as both genders ate standard chow based on their hunger level (Buczek et al., 2020). Such study examined the activation and signaling of orexin neurons to determine the neuronal mechanisms of pleasurable eating. The researchers found that orexin neurons were activated by food and fasting in both genders, and blocking OX1R signaling with SB334867 reduced the consumption of palatable food in both hungry and satiated rats of both genders. These findings suggest that there are sex differences in pleasure-seeking eating, with females being more susceptible to overeating palatable food regardless of their hunger level, and orexin is a crucial neuropeptide mechanism involved in pleasurable eating for both genders (Buczek et al., 2020).

Notably, these findings are in line with the upregulation of orexin signaling in the brain of rats exposed to drugs of abuse, including cocaine, morphine, fentanyl and alcohol (James et al., 2019), or in the plasma of humans treated with antipsychotic medications (Chen et al., 2019). On the contrary, broader-scale studies have reported that narcolepsy, which is associated with reduced orexin activity, is associated with increased impulsivity and binge-eating behaviors (Dimitrova et al., 2011; van Holst et al., 2016) by highlighting the dichotomy of roles between OX1R and OX2R in mediating food seeking and energy expenditure, respectively. For that reason, it could be that binge-induced plasticity of the orexin system results in an imbalance between the receptor for OXA (OX1R) and OXB (OX2R) signaling that promotes excessive food intake via the OX1R. The most common eating disorder among adults is BED, characterized by recurrent episodes of uncontrollable overconsumption of palatable food. BED is associated with various comorbidities, including obesity, MDD, and substance use disorder, and has been linked to increased levels of impulsivity. However, the neurobiological basis of BED is still unclear. Binge eating occurs outside of homeostatic needs and is related to hedonic consumption of palatable food. The NAc shell, a major brain structure controlling hedonic feeding and regulating impulsive action, is of particular interest. Schuller and Koch studied the impact of the impulsivity on the development of binge eating-like feeding and the role of orexins in the NAc shell by exploiting a rat's model based on a limited access using pure vegetable fat. All animals, regardless of their impulsivity trait, developed stable binge eating-like palatable food intake. Alterations in orexinergic transmission in the NAc shell of rats bingeing on pure fat were reported, which was supported by lower density of OX1R in the NAc shell of rats with binge eating-like feeding behavior (Schuller and Koch, 2022).

Taken together, data from preclinical and human research suggest that orexin signals regulate both homeostatic and hedonic eating and may serve as useful novel pharmacotherapies for the treatment of eating disorders. Preclinical data report a successful study about the potential efficacy of single orexin receptor antagonists (SORA) as selective blockade of the OX1R to manage food craving and intake in BN and BED. Although several SORAs are under the drug development pipeline, no such compounds are yet approved for human therapy. However, a strong rationale supports a possible repurposing of already approved DORAs in the treatment of BED patients. In addition to reducing food-seeking via actions at OX1R, these compounds may have also an additional indirect benefit for improving binge eating by normalizing sleep pattern in BED patients via OX2R. Indeed, animal studies indicate efficacy of suvorexant, a class of insomnia agents, as indicated in section 3, and its analogs in reducing drug-seeking and normalizing abstinence-related sleep outcomes (Gentile et al., 2018). With respect to BED, only one study has reported anti-bingeing effects and strong hypnotic properties of DORA in rats although bingeing and sleep outcomes were studied in separate groups of rats (Piccoli et al., 2012). Moreover, even though no clinical studies have examined the effect of DORAs on binge eating per se, one report showed efficacy for suvorexant in patients with nighttime eating (Ono et al., 2018). Thus, there is a clear need for both preclinical and clinical studies to directly test the efficacy of DORAs on both bingeing and sleep outcomes in BED. As a consequence, pharmacotherapies that ameliorate orexin signaling might have therapeutic value in eating disorders, mainly AN and BED; in particular the DORA SB649868, but not the selective OX2R antagonist JNJ10397049, reduces compulsive food overconsumption (Piccoli et al., 2012), confirming a key role for OX1R signaling in the compulsive eating (Pich and Melotto, 2014). On the contrary, the OX1R antagonist SB334867 inhibits compulsive eating behavior in rats exposed to chronic stress induced by food restriction, while it is unable to inhibit highly palatable food intake in control animals unexposed to cyclic food restriction (Piccoli et al., 2012). This data reinforces the functional dichotomy of orexin receptors since DORAs might reduce binge eating outcomes by simultaneously reducing food craving via actions at OX1R and normalizing sleep by reducing signaling at OX2R.

In conclusion, many pieces of evidence from preclinical studies and clinical data indicate that eating disorders share a common, yet non-diagnostic, incidence with sleep disorders, particularly insomnia despite limited evidence from studies in BED patients pointing to a positive correlation between the incidence of insomnia and eating disorders. Animal models of BED, by allowing more invasive interrogation of the neurobiological substrates, should be exploited to begin to understand whether excessive eating and dysregulated sleep share common orexin pathways, which are central to the regulation of both hedonic food-seeking and arousal/wakefulness.

7. Orexins and schizophrenia

Schizophrenia is a complex disorder affecting 1% of the world population, characterized by perceptual alterations, delusions, hallucinations, anhedonia, asociality, and cognitive impairments (McCutcheon et al., 2020). The pathophysiology of schizophrenia is explained through diverse complementary hypotheses, including the classically-accepted dopaminergic hyperfunction and glutamatergic hypofunction (Buck et al., 2022; Howes et al., 2015). Nevertheless, some other players have also been described to be altered in such disorder, like the orexin system (Lin and Huang, 2022). In this sense, several studies have reported

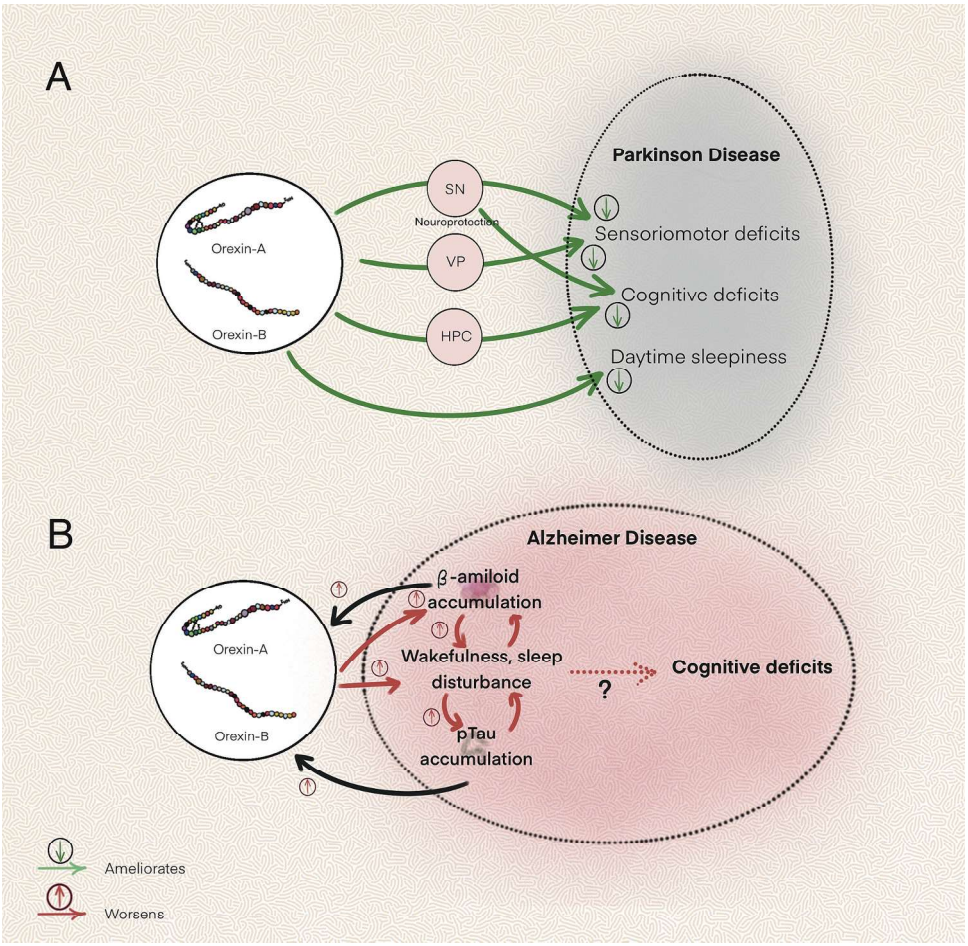

Fig. 4. Orexins are a potential therapeutic target for Parkinson Disease (PD) and Alzheimer Disease (AD). (A) Orexins may exert beneficial effects on PD symptoms by neuroprotecting dopaminergic neurons within the substantia nigra and through other brain regions. (B) In contrast, high orexin levels in AD may increase β-amyloid and tau accumulation by promoting wakefulness among other mechanisms, which in turn increases orexin levels in a positive feedback loop. The consequences for cognitive decline are still unclear. HPC, hippocampus; SN, substantia nigra; VP, ventral pallidum.

unclear correlations between the orexin system and different schizophrenia-like parameters. For example, OXA plasma levels and postmortem hypothalamic OXA were significantly decreased in schizophrenia patients compared to healthy controls, as well as cortical OX2R mRNA only in female individuals. However, male schizophrenia patients showed a trend of increased cortical OX1R and OX2R mRNA expression, compared to male controls (Lu et al., 2021). Regarding clinical traits, negative and disorganized symptoms of schizophrenia were associated with increased OXA plasma levels (Chien et al., 2015; Liu et al., 2020), although this correlation was not found in another study with Japanese individuals (Tsuchimine et al., 2019). On the other hand, schizophrenia treatment with antipsychotics was observed to increase OXA plasma levels, in comparison with drug-free patients (Chen et al., 2022). Overall, clinical investigations have reported inconsistent findings in an attempt to elucidate the involvement of the orexin system in schizophrenia. Some preclinical studies have addressed this psychiatric disorder with different animal models to better understand the role of the orexin system. A key element in schizophrenia is the disruption of the sensorimotor gating, that can be evaluated through the prepulse inhibition (PPI) test, in which a weak stimulus attenuates the startle response to a subsequent stronger startle stimulus. This inhibitory response has been widely described to be impaired in patients with schizophrenia, as well as in other psychiatric diseases (e.g., HD, obsessive–compulsive disorder) (Haß et al., 2017; Kohl et al., 2013). Indeed, reduced PPI is considered a biomarker of schizophrenia (Mena et al., 2016). An interesting study by Öz and colleagues revealed that OXA administration decreased the PPI response in naive rats, whereas lower doses of OXA were able to restore sleep-deprivation-induced impairment of PPI. These results demonstrated the involvement of the orexin system in PPI, with opposite effects on non-sleep-deprived and sleep-deprived rats (Öz et al., 2018). Conversely, another study with orexin-deficient mice confirmed the key role of the orexin system in the modulation of PPI in the opposite direction, since these animals presented remarkable deficits in the sensorimotor gating. Moreover, amphetamine-induced disturbances in the PPI of wild-type mice were not present in homozygous orexin-deficient mice, thus suggesting the participation of the orexin system in neuropsychiatric disorders associated with sensorimotor gating deficiencies, like schizophrenia (Demidova et al., 2022).

Despite the unclear role of the orexin system in this psychiatric disorder, some studies have already presented evidence about the beneficial effects of orexin receptors blockade in different schizophrenia endophenotypes. According to this, the DORA TCS-1102 normalized dopaminergic activity in a rat model of aberrant dopamine system function, as measured by in vivo electrophysiology after administration of such antagonist (Perez and Lodge, 2021). Also, a recent study has reported therapeutic properties of the DORA filorexant (MK-6096) on attentional impairments in an NMDA receptor hypofunction model of schizophrenia (Maness et al., 2023). These new and limited findings postulate the orexin system as a novel site of therapeutic interventions. Hopefully, future research will decipher the precise role of the orexin system in schizophrenia, a multifactorial psychiatric disorder that needs to be better understood.

8. Orexins and neurodegenerative diseases

During the last decade, the orexinergic system has gained interest as a possible target to treat neurodegenerative diseases. An increasing body of evidence supports that orexin neurons, just as other neuronal

populations, are not exempt of damage throughout the progression of diseases such as Parkinson disease (PD), Alzheimer disease (AD), Huntington disease (HD) or multiple sclerosis (MS). Altered orexinergic transmission may explain many of the clinical manifestations of these neurodegenerative disorders. But most importantly, orexin peptides might act as active players at the root of the neurodegenerative pathophysiology itself (Fig. 4).

As a significant portion of neurodegenerative disorders develop during aging, it is essential to differentiate the malfunctioning of orexinergic transmission in healthy aging from that occurring in pathological conditions. The number of orexinergic neurons decreases by 25% from childhood to maturity (60 years old or above) (Hunt et al., 2015). Despite this loss, recent research has shown that these neurons become hyperexcitable and overexpress orexin peptides in aged mice (Li et al., 2022). These alterations facilitate orexin neurons to reach the sleep-to-wake transition threshold, driving sleep fragmentation during aging (Li et al., 2022). Although most studies addressing the role of orexins in age-related neurodegenerative conditions include age-matched controls, having this scenario in mind may help to better understand the entire picture.

8.1. Parkinson disease

PD is a neurodegenerative disorder characterized by motor symptoms, such as tremor, muscular rigidity and bradykinesia, as well as non-motor symptoms, including emotional and cognitive alterations, and sleep disorder. The first evidence pointing to orexins as possible key players in PD's pathophysiology emerged from clinical works reporting reduced orexin levels in ventricular CSF of PD patients (Drouot et al., 2003; Fronczek et al., 2007). Other studies, however, showed that orexin levels were within the normal range in the lumbar CSF of parkinsonian patients (Baumann et al., 2005; Yasui et al., 2006; Compta et al., 2009). Notably, most research reporting unaltered CSF orexin levels had obtained CSF samples by lumbar punction (Overeem et al., 2002; Baumann et al., 2005; Yasui et al., 2006; Compta et al., 2009), which might be less sensitive to orexin variations than ventricular samples, as suggested by the difficulties to detect circadian orexin fluctuations in lumbar CSF samples (Poceta et al., 2009). The assessment of CSF orexin levels at different timepoints or disease stages resulted crucial to unravel that orexin levels are inversely correlated with disease severity and progression, as well as with cognitive dysfunction, daytime sleepiness and sleep attack appearance (Asai et al., 2009; Wienecke et al., 2012). Consistently, PD patients showed less orexin immunoreactive neurons compared to matched controls (Fronczek et al., 2007; Thannickal et al., 2007), a phenomenon also observed in a rat model of PD (Cui et al., 2010). Thus, loss of orexin neurons and hypofunctional orexinergic transmission occur in PD, particularly during late stages, contributing to some of the clinical manifestations of the disease.

The hallmark of PD is the selective degeneration of dopaminergic neurons in the substantia nigra. This brain region receives dense orexinergic innervation and expresses high levels of orexin receptors (Hrabovszky et al., 2013; Bensaid et al., 2015). Accordingly, local infusion of OXA and OXB within the substantia nigra pars compacta increased spontaneous physical activity in rodents (Kotz et al., 2006) and promoted spontaneous firing of nigral dopamine neurons through both OX1R and OX2R (Liu et al., 2018a). It has been suggested that degeneration of nigral dopamine neurons may occur more easily if they stay electrically inactive (Douhou et al., 2001; Salthun-Lassalle et al., 2004; Michel et al., 2013). Hence, maintaining a functional orexinergic tone might preserve basal firing of dopaminergic neurons and reduce their vulnerability to degenerate (Berhe et al., 2020). Indeed, orexin peptides have been shown to exert a neuroprotective effect on dopaminergic neurons in cultured cells (Wang et al., 2021). Thus, OXA attenuated the degeneration of dopaminergic-like SH-SY5Y cells induced by 6-hydroxydopamine or 1-methyl-4-phenylpyridinium, two *in vitro* models of PD (Feng et al., 2014; Pasban-Aliabadi et al., 2017). This effect was mediated by OX1R signaling (Pasban-Aliabadi et al., 2017). Interestingly, in rat midbrain cultures where dopaminergic neurons spontaneously and progressively degenerate as they mature, OXB increased the survivability through OX2R, but not by OX1R (Guerreiro et al., 2015).

The neuroprotective effect of orexins has also been reported in animal models of PD. In mice, OXA reduced 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced loss of dopaminergic neurons in the substantia nigra and normalized the striatal dopaminergic fibers, an effect that translated into an improvement of spatial memory and motor activity. These observations were dependent on OX1R signaling and involved an increase of brain-derived neurotrophic factor (BDNF) protein levels in dopaminergic neurons (Liu et al., 2018b). Consistently, BDNF presence in the substantia nigra is known to prevent dopaminergic neurons from degeneration (Fumagalli et al., 2006). In addition, OXA central administration ameliorated 6-OHDA-induced sensorimotor impairments in rats, as shown by improved performance in rotarod and hanger test (Hadadianpour et al., 2017). Administration of an OX1R antagonist instead of OXA, in contrast, worsened the phenotype of these parkinsonian-like rats (Hadadianpour et al., 2017). Orexins may improve motor performance also by acting on brain regions alternative to the substantia nigra, since bilateral orexin microinjection within the globus pallidus, a key nucleus in voluntary motor control, alleviated motor deficits in MPTP-induced parkinsonian-like mice by increasing the firing of pallidal neurons through an OX1R-dependent mechanism (Xue et al., 2016; Wang et al., 2019b).

Non-motor symptoms observed in animal PD models also appear modulated by orexinergic transmission. A53T mice, a transgenic mouse model of PD, display early social cognitive alterations and hippocampus-dependent memory impairment (Stanojlovic et al., 2019a, 2019b). Chemogenetic activation of orexin neurons reversed alterations in sociability in this mouse PD model, as well as spatial and object recognition memory (Stanojlovic et al., 2019b). OXA microinjection in the hippocampus of A53T mice also ameliorated performance in these hippocampus-dependent memory tasks (Stanojlovic et al., 2019a). In agreement, 6-OHDA-induced parkinsonian-like rats display similar memory impairments associated to reduced orexinergic projections within the hippocampus (Oliveira et al., 2020), which further supports the relevance of hippocampal orexinergic transmission to prevent this particular phenotype trait.

In summary, orexins progressively decline during PD and this may contribute to some clinical manifestations of the disease, such as excessive daytime sleepiness. In addition, since orexins play a neuroprotective function over nigral dopaminergic neurons, deficient orexinergic transmission in turn may worsen disease severity and progression. As shown in preclinical models, orexin replacement therapy could potentially attenuate both motor and non-motor clinical manifestations of PD and delay disease progression (Fig. 4).

8.2. Alzheimer disease

AD constitutes the most common neurodegenerative disease. The clinical manifestations of AD include progressive loss of memory and other cognitive functions. AD neuropathological hallmarks include neuronal loss, the intraneuronal presence of neurofibrillary tangles rich in hyperphosphorylated Tau protein, and the extracellular deposits (i.e., neuritic plaques) of β-amyloid (Aβ) filaments (Lane et al., 2018).

Similar to PD, clinical findings point to an orexinergic dysregulation in AD, as suggested by abnormal CSF orexin levels in AD patients. However, discrepancies between studies do not allow robust conclusions with this regard (Treu and Plante, 2021). Thus, some reports show increased lumbar CSF orexin levels in AD (Liguori et al., 2014, 2016; Gabelle et al., 2017), whereas others sustain that orexin levels remain within the normal range (Slats et al., 2012; Schmidt et al., 2013) or even below in ventricular postmortem samples (Fronczek et al., 2012). Importantly, studies showing unaltered CSF orexin levels in AD were, nonetheless, sensible enough to detect circadian (Slats et al., 2012) or

sex-related (Schmidt et al., 2013) orexin variations. Still, most studies show a common finding: high CSF orexin levels are associated with decrease of REM and sleep efficiency (Liguori et al., 2014, 2016), whereas excessive daytime sleepiness occurs when orexin levels are low (Friedman et al., 2007; Fronczek et al., 2012). Both cases have been reported in AD, but sleep disturbance is the most concerning due to its exacerbation of cognitive decline (Wang and Holtzman, 2020).

Orexins are also associated to the rise of neuropathological biomarkers of AD. CSF orexin levels positively correlate with Aβ42 presence in AD patients (Liguori et al., 2016; Gabelle et al., 2017). Consistently, knocking out the orexin gene in a transgenic AD mouse model decreased the formation of Aβ plaques and attenuated sleep fragmentation (Roh et al., 2014). Rescuing orexinergic neurons in the same animals increased wakefulness and induced Aβ accumulation (Roh et al., 2014). Indeed, Aβ levels in interstitial fluid correlated with wakefulness and increased during sleep deprivation or during orexin infusion in mice, whereas repeated DORAs reduced Aβ plaque formation (Kang et al., 2009). This has been hypothesized to occur at least through two mechanisms (Dauvilliers, 2021): i) orexins may facilitate Aβ production, since Aβ is primarily produced during wakefulness (Vyazovskiy et al., 2009; Ju et al., 2014), and ii) orexins may interfere with Aβ clearance, which is much faster during sleep time (Xie et al., 2013), and requires phagocytosis and autophagic flux in microglia, processes disrupted by orexins resulting in impaired Aβ degradation *in vitro* (An et al., 2017). Interestingly, emerging evidence suggests that the association between Aβ and orexins/wakefulness is bidirectional, since high Aβ presence in brain tissue increased both OXA levels and the awaked time in AD mice (Chishti et al., 2001; Liu et al., 2019; Zhao et al., 2022). Hence, a positive feedback loop may exist between Aβ accumulation and orexinergic function/sleep impairment, which highlights the relevance of targeting the orexin system for interrupting this vicious cycle.

Orexinergic dysregulation also worsens tauopathy. CSF orexin levels of AD patients are positively correlated with tau and phosphorylated tau (Deuschle et al., 2014; Liguori et al., 2020), which in turn correlate to sleep dysfunction (Liguori et al., 2020), although these could imply just concomitant phenomena and the lack of long time-course CSF orexin determinations dissuades from drawing robust conclusions with this regard. Interestingly, an *in vitro* study revealed that pretreatment with a tau inhibitor reversed the Aβ-induced increase in tau, phosphorylated tau and OXA expression (Liu et al., 2019), pointing to a network of reciprocal molecular interactions that contribute to AD pathophysiology.

Although sleep disruption in AD is a key matter to target due to its association with cognitive decline, the connection between orexin levels and cognitive function in AD remains inconclusive, as both positive (Shimizu et al., 2020) and negative (Liguori et al., 2014) correlations have been reported in the clinical setting. Basal forebrain cholinergic neurons, critical for cognitive function, are degenerated in AD (Shekari and Fahnestock, 2021). Orexin neurons activate these cholinergic neurons through direct synapses (Li and de Lecea, 2020), and local OXA infusion within the basal forebrain increases cognitive function (Calva et al., 2019; Zajo et al., 2016). Intranasal orexin administration has even been proposed to potentially treat age-related cognitive decline due to its cholinergic enhancing effects (Erichsen et al., 2021). However, central OXA administration in AD-like mice worsened cognitive deficits in the Morris water maze and promoted Aβ accumulation as well as mitochondrial impairment (Li et al., 2020). Further research will be required to refine manipulations of the orexin system so we can avoid its deleterious effects (i.e., worsening Aβ and tau pathology as well as sleep disturbance) while enhancing the potential cognitive benefits (Fig. 4).

8.3. Other neurodegenerative diseases

HD is an inherited neurodegenerative disease caused by a mutation in the huntingtin gene. The clinical manifestations of this disorder are progressive motor impairment (i.e., chorea, lack of coordination), cognitive decline, emotional disturbances and desynchronized sleep-wake rhythms (Walker, 2007). Although it is mostly known as a basal ganglia disease, other brain regions are deeply affected in HD, including the hypothalamus (Petersén and Gabery, 2012). Consistently, post-mortem examinations of brain tissue affected by HD revealed a loss of orexin neurons when compared to controls (Peterseén et al., 2005; Aziz et al., 2008; Gabery et al., 2010). This has also been observed in rodent models of HD (Williams et al., 2011; Gabery et al., 2012). Similarly, orexin mRNA levels were reduced in the hypothalamus of HD patients and HD-like mice (Baldo et al., 2019). However, orexinergic loss coexisted with apparently unaltered CSF orexin levels in the clinical setting (Gaus et al., 2005; Meier et al., 2005; Baumann et al., 2006), and an electrophysiological study in brain slices from R6/2 mice, a rodent HD model, sustained that intrinsic firing properties of orexinergic cells remained unaltered and functional (Williams et al., 2011). This raises the question of whether orexin loss involves clinically relevant consequences. A few studies in mice models suggest that it does. Indeed, R6/2 mice show an abnormal sleep/wake pattern, featured by narcoleptic-like episodes during the active phase (Peterseén et al., 2005) and sleep fragmentation during the resting phase, leading to detrimental cognitive performance (Cabanas et al., 2019). Previous studies showed that restoring normal sleep-wake cycles can improve cognitive function in HD mice (Pallier and Morton, 2009). Interestingly, an acute administration of the DORA suvorexant was sufficient to improve sleep, and 5-day treatment attenuated cognitive deficits in R6/2 mice (Cabanas et al., 2019). In addition, depressive and anxiety-related symptoms of HD were reproduced in a mouse model expressing the human full-length mutant huntingtin. Orexin neurons suffered from cellular atrophy in these mice, but when mutant huntingtin was inactivated within the hypothalamus, the development of depressive-like (but not anxiety-like) phenotype was prevented (Hult Lundh et al., 2013), suggesting a possible role for orexin transmission in the psychiatric manifestations of HD. In summary, orexinergic dysregulation may contribute to multiple aspects of HD symptomatology.

The anti-inflammatory and neuroprotective properties of orexins have led to explore the possible link between this system and MS, an inflammation-related autoimmune disease in which demyelination of the CNS is the key neuropathological feature, eventually resulting in neurodegeneration (Cotsapas et al., 2018). Besides muscle spasms, tingling and pain, the most common symptoms associated with MS are fatigue and sleep disturbances (Bøe Lunde et al., 2012; Manjaly et al., 2019). Some case reports found that patients with MS-associated hypothalamic lesions had undetectable CSF orexin levels and displayed hypersomnia or fatigue (Kato et al., 2003; Oka et al., 2004). Although altered orexin levels were not confirmed in MS patient cohort studies due to inter-individual variability (Knudsen et al., 2008; Papuć et al., 2010; Constantinescu et al., 2011), low orexin levels did correlate with daytime sleepiness and fatigue, as well as with disease progression and motor system affectation (Gencer et al., 2019). Some preclinical studies employing experimental autoimmune encephalomyelitis (EAE, the most commonly used model for MS) suggest that orexin peptides could act as potent anti-inflammatory agents in MS. Central (Fatemi et al., 2016) or systemic (Becquet et al., 2019) OXA administration attenuated the clinical symptoms of EAE and improved histological markers of disease severity and progression. OXA inhibited infiltration of inflammatory cells, decreased glial activation, and promoted myelin preservation (Fatemi et al., 2016; Becquet et al., 2019). Thus, orexin peptides might be useful to slow down MS progression by inhibiting neuroinflammation and subsequent neurodegeneration.

Lastly, a couple of studies have explored the role of orexins in amyotrophic lateral sclerosis (ALS), a condition featured by motor neuron degeneration and subsequent muscle weakness and paralysis. Although apparently unaltered CSF orexin levels were found in ALS patients (van Rooij et al., 2009), postmortem examination of brain tissue recently revealed a global hypothalamic atrophy and loss of orexin-expressing neurons, which correlated with altered eating behavior

(Gabery et al., 2021). Similarly to other neurodegenerative diseases, however, further studies assessing CSF orexin levels throughout the time-course of disease progression and over different patient profiles are required before drawing any conclusions. On the other hand, a mouse model of ALS displayed upregulated orexins that positively correlated with awake time (Liu et al., 2015). These studies encourage further research to unravel the involvement of orexins in ALS clinical manifestations.

9. Future perspectives

The orexin system presents a deep involvement in the control of specific biological functions, as accurately updated in this review. However, many issues remain to be clarified to completely profit the wide range of therapeutic opportunities, provided by this neurotransmitter system. To date, more than 140 clinical trials have been or are currently testing several orexin-targeting candidates for different pathological conditions, mainly sleep disturbances, substance use disorders and cognitive impairments. Also, other alterations such as diabetes, chronic pain and hyperemesis are presently assessed, as posted in clinic altrials.gov. Moreover, preclinical research with orexins has opened up the range of unexpected potential therapies for many other disorders. Beyond the pathological conditions addressed in the present review, recent evidence suggests that orexins could also play an important role in the pathophysiology of several tumors since orexin receptors have been detected in different types of neoplasms. Specially, in gastrointestinal tumors, but also cervix, prostate, kidney, adipose tissue, testicles, and hematological malignances (e.g., lymphomas). A positive correlation has been found between orexin receptors and the progression of cancer, thus indicating that orexin antagonism might have a potential therapeutic effect (Alain et al., 2021; Couvineau et al., 2022). Interestingly, a role for OXA has been recently described in the gut-brain communication. Microbiome has emerged as a new promising target that can modulate neurochemistry and behavior, by interacting with the CNS through different mediators. OXA transmits signals to the brain on nutritional status and inflammation and responds to infections by reducing intestinal permeability and neuroinflammation (Mediavilla, 2020). Furthermore, research in the field of orexins still has a long way to go to clearly elucidate their role in several pathologies, specially the poorly understood rare diseases. Various studies have already investigated the role of the orexin system in some rare diseases, such as Perry syndrome (Mishima et al., 2017), rapid-onset obesity with hypothalamic dysfunction, hypoventilation, and autonomic dysregulation (ROHHAD) (Dhondt et al., 2013; Barclay et al., 2016), and Niemann-pick disease type C (Imanishi et al., 2020).

On the other hand, it is also important to dispose of effective tools to modulate the different components of the orexin system. In this regard, most of the molecules used in clinical and preclinical studies exert an antagonism on both or a single orexin receptor. However, only a few agonists have been so far synthesized (Nagahara et al., 2015; Hong et al., 2021), despite the potential therapeutic properties for some disorders, such as narcolepsy, Parkinson disease, and mood disorders. Peptide agonists have failed to achieve a sufficient brain exposure. Conversely, non-peptide, low molecular, bioavailable and brain penetrant orexin receptor agonists are an alternative strategy that will probably get a greater voice in the next years.

Despite the higher prevalence of psychiatric disorders affecting women in comparison with men, most of the studies in orexin research have been performed only with male individuals. This constitutes a clear limitation for current investigations since constitutive sex differences in the orexin system have already been reported. In this sense, naïve female rats present higher basal prepro-orexin expression and activation of orexinergic neurons than males (Grafe et al., 2017a). Moreover, orexin-expressing neurons in female rats have significantly more dendritic spines than those in male individuals, and most of them were reported to be mature spines (Grafe et al., 2019). Such structural variations might explain many other sex-differences in orexin-related endophenotypes. For instance, female rats failed to habituate to repeated stress, thus inducing impaired cognitive flexibility, compared to male rats. These deficits were observed to be mediated by an overactivity of the orexin system in female rats, which was significantly decreased in the opposite gender (Grafe et al., 2017a). Another interesting study with orexin-deficient mice also revealed sex differences in the regulation of cognitive flexibility by the orexin system (Durairaja and Fendt, 2021). Taken these results into account, further research should address sex differences in orexin-mediating functions in order to better clarify the role of the orexin system in the different psychiatric disorders.

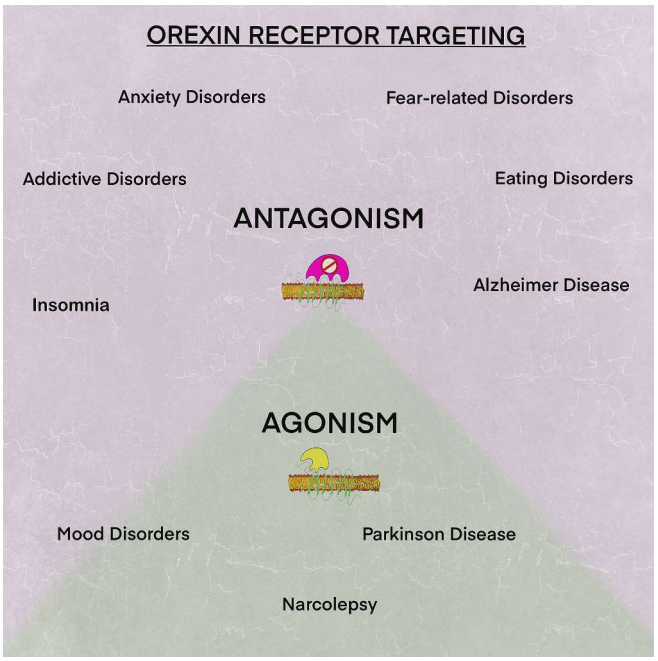

Fig. 5. Main neuropsychiatric and neurodegenerative diseases associated with the orexin system, which activation or blockade are suggested to ameliorate the disease, based on preclinic and clinical studies.

10. Conclusions

The pharmacological and biochemical studies described in the present review support an important involvement of orexins in different psychiatric and neurodegenerative diseases. Considering results obtained from basic and clinical research, activation of the orexin system could be targeted for the treatment of narcolepsy, major depressive disorder, or Parkinson's disease. On the contrary, orexin activity blockade could be useful to treat addiction, anxiety, fear-related disorders, eating disorders, or Alzheimer's disease (Fig. 5). Currently, three orexin receptor antagonists (suvorexant, lemborexant and daridorexant) have been approved for the treatment of insomnia. Although the route from basic science discovery to development of approved treatments is slow, new pharmacological agents based on the orexin system will be probably developed in the near future, given the intense activity in this field of research.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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